

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020687Orig1s020

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 20687

SUPPL # 020

HFD # (b) (6)

Trade Name Mifeprex

Generic Name mifepristone

Applicant Name Danco Laboratories, LLC

Approval Date, If Known March 29, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2) – efficacy supplement

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20687

NDA# 202107

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The applicant submitted published literature for this efficacy supplement.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

The applicant submitted published literature for this efficacy supplement.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES

!
!
! NO
! Explain:

Investigation #2

IND #

YES

!
!
! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

The applicant did not provide financial support nor sponsored any of the studies that were submitted for review. This was a complete literature based application.

=====
Name of person completing form: (b) (6)
Title: (b) (6)
Date: March 10, 2016

Name of (b) (6) signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

(b) (6)

From: (b) (6)
Sent: Thursday, March 17, 2016 1:34 PM
To: (b) (6)
Subject: REMS documents
Attachments: Mifeprex_Prescriber_Enrollment_Form MarkupForDanco_3.14.16.docx; NDA 020687
REMS doc 2 23 16 markupForDanco_3.9.16.docx

(b) (6)

Please find attached the documents for the REMS. Can you please have these back to us by Monday?

Thanks,

(b)
(6)

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/s/

(b) (6)

03/21/2016

(b) (6)

From: (b) (6)
Sent: Wednesday, March 09, 2016 2:56 PM
To: (b) (6)
Subject: Draft Mifeprex label - FDA revision
Attachments: 20687s020 label VERSION sent to Sponsor 3.9.16.doc

(b) (6)

Attached is the draft label for your review. In addition to the revisions in the label, we have additional requests below. Please use this reversion and if you agree w/our changes, you should accept the track changes, and delete any corresponding comments from us. If you disagree, or revise, you should show it in track changes with a comment giving your rationale. We would like to have the label or at least sections that you have finished by COB March 11, 2016. If this is an issue, please let me know as soon as possible. The REMS documents will follow.

Re: Section 6:

1. You base Section 6.1 on Winikoff 2008 and 2012 and Middleton 2005. Provide the rationale for why you selected these 3 studies (and why you did not include other studies) to provide the data for this section.
2. It is important to provide AR data based, at least in part, on studies that included women up to GA of 70 days. We believe that the following studies may be appropriate for inclusion in this section:

Middleton 2005, Blum 2012, Louie 2014, Pena 2014, Chong 2012, Winikoff 2012 & Sanhueza Smith 2015

Indicate whether you agree and, if you do not, why not.

3. When we reach agreement on the studies on which this section will be based, it is important that you provide a high-level summary describing the studies (basic demographic information, major trial exclusions [e.g., if smokers were excluded], etc.). Refer to the Adverse Reactions guidance.
4. Clarify the source of the information included in Table 1 – for example, why are the Ns different for different ARs? If the % data are pooled from several studies, explain how you did this (e.g., weighted average, etc.). The text states that ARs occurring in $> \frac{(b)(4)}{(4)}\%$ of women are shown, but the lowest frequency event is $\frac{(b)(4)}{(4)}\%$ - is it correct that no ARs occurred with frequency between $0 - \frac{(b)(4)}{(4)}\%$ in these 3 studies? We can accept a higher threshold for reporting ARs in the table (e.g., $\frac{(b)(4)}{(4)}\%$), but you should provide a justification for what you propose.
5. We have removed the Warning regarding changes in $\frac{(b)(4)}{(4)}$, and our impression of the old clinical data suggests that there were no reasons for clinical concern about this issue. If you disagree, and believe that it is important to inform providers about $\frac{(b)(4)}{(4)}$ changes, add a statement to Section 6.1.

6. To the extent possible, add information about serious adverse reactions (e.g., bleeding, infection, etc. that met criteria for being considered a SAR) that occurred in the studies discussed in this section, and about adverse reactions that led to premature discontinuation of the study. We acknowledge that this information may not be available for some/all of the studies discussed.

Re: Section 14:

1. Identify which studies you have used to provide the pooled data in this section, and provide your rationale for why you selected these studies (and why you did not include other studies) to provide the data for this section.
2. Provide us with the calculations you performed to arrive at the pooled data presented in Table 4 (b) (4)
3. Clarify whether the numbers provided for the “worldwide” trials also include data from the US trials; it would be preferable to present this as US and non-US data.
4. It is important to provide efficacy data based, at least in part, on studies that included women up to GA of 70 days.

5.

(b) (4)

6.

7.

8. We request that you provide data describing the effectiveness of a second dose of misoprostol in women who did not have a complete abortion following the initial dose regimen.

Other comments/questions are embedded within the labeling itself.

Thanks,

(b) (6)

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/s/

(b) (6)

03/17/2016

(b) (6)

From: (b) (6)
Sent: Wednesday, February 24, 2016 12:19 PM
To: (b) (6)
Subject: Information Request

(b) (6)

Please amend your application to include the following references:

Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. [Contraception](#). 2010 Apr; 81(4):269-74.

Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015; 125(1): 175-183.

Thanks,

(b)
(6)

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/s/

(b) (6)

03/03/2016

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-
- Proposed Indication: Medical termination of intrauterine pregnancy through (b) (4) days gestation
 - The Division clarified that this product triggered PREA because a new dosing regimen was identified based on a literature review. There were no clinical trials conducted by the sponsor in seeking this change in dosing regimen. However, the literature review included safety and efficacy data in over 300 adolescent patients that support approval in all post-menarchal females.
 - (b) (6) *Recommendations:*
 - (b) (6) agreed with the Division to grant a partial waiver in patients ages birth to 12 years of age who are pre-menarche. The division provided an adequate assessment for patients who are post-menarche.

(b) (6)

From: (b) (6)
Sent: Wednesday, December 02, 2015 3:11 PM
To: (b) (6)
Subject: IR to Danco for additional references
Attachments: 12-2-15 IR re more References.doc

(b) (6)

Please see the attached information request? Let me know if you have any questions.

Thanks,

(b)
(6)

Information Request (IR): References for Danco to submit to NDA 020687/S-020

Date: December 3, 2015

1. Cleland K, Smith N. Aligning mifepristone regulation with evidence: driving policy change using 15 years of excellent safety data. *Contraception* 2015;92:179-81.
2. Gold M, Chong E. If we can do it for misoprostol, why not for mifepristone? The case for taking mifepristone out of the office in medical abortion. *Contraception* 2015;92:194-6.
3. Swica Y, Chong E, Middleton T, et al. Acceptability of home use of mifepristone for medical abortion. *Contraception* 2013;88:122-7.
4. Chong E, Frye LJ, Castle J, Dean G, Kuehl L, Winikoff B. A prospective, non-randomized study of home use of mifepristone for medical abortion in the U.S. *Contraception* 2015;92:215-9.
5. Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70days gestation. *Contraception* 2015;92:197-9.
6. Lynd K, Blum J, Ngoc NT, Shochet T, Blumenthal PD, Winikoff B. Simplified medical abortion using a semi-quantitative pregnancy test for home-based follow-up. *Int J Gynaecol Obstet* 2013;121:144-8.
7. Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012;86:251-6.
8. Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015;22:75-82.
9. Pazol K, Creanga AA, Burley KD, Jamieson DJ. Abortion surveillance - United States, 2011. *MMWR Surveill Summ* 2014;63:1-41.
10. Jones RK, Jerman J. Abortion Incidence and Service Availability In the United States, 2011. *Perspect Sex Reprod Health* 2014.
11. Jones RK, Kooistra K. Abortion incidence and access to services in the United States, 2008. *Perspect Sex Reprod Health* 2011;43:41-50.
12. Grossman D, Goldstone P. Mifepristone by prescription: a dream in the United States but reality in Australia. *Contraception* 2015;92:186-189.
13. Grossman DA, Grindlay K. Alternatives to ultrasound for follow up after medical abortion: a systematic review. *Contraception* 2011;83:504-10.
14. Grossman DA, Grindlay K, Buchacker T, Potter JE, Schmertmann CP. Changes in service delivery patterns after introduction of telemedicine provision of medical abortion in Iowa. *Am J Public Health* 2013;103:73-8.
15. Maarit N, Suhonen S, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. *BJM* 2011;342:d2111.

16. Raymond EG, Grossman D, Wiebe E, Winikoff B. Reaching women where they are: eliminating the initial in-person medical abortion visit. *Contraception* 2015;92:190-93.

17. Puri M, Tamang A, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reprod Health Matters* 2015;22:94-103.

In addition, please submit the requested references that were not sent from the IR dated October 30, 2015.

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/s/

(b) (6)

12/02/2015

(b) (6)

From: (b) (6)
Sent: Friday, October 30, 2015 10:29 AM
To: (b) (6)
Subject: Information Request
Attachments: 20687s20 IR 10.30.15.doc

(b) (6)

Please see the attached information request.

Thanks,

(b)
(6)

Clinical Request:

We are in the process of reviewing your NDA 20687/S-020. We are interested in whether adherence to the medication regimen and to follow-up is comparable between adolescents <17 years old and adult populations.

You provide data from the article Gatter M et al on loss to follow-up compared among age groups. (Gatter et al Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015;91:269-273.) We would be interested to know whether you have additional information on adherence to the medication regimen compared between age groups (< 17 vs. ≥17 years) in that study.

Further, regarding options for follow-up of medication abortion, you provide several articles.

1. *Cameron ST et al. Telephone follow-up and self-performed urine pregnancy testing after early medical abortion: a service evaluation. Contraception 2012;86:67-73.*
This study appears to include subjects at least 16 years old.
2. *Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam. Obstet Gynecol 2014;123(1):88-95.*
This study appears to include subjects at least 15 years of age.
3. *Grossman D et al. Accuracy of a semi-quantitative urine pregnancy test compared to serum beta-hCG measurement: a possible screening tool for ongoing pregnancy after medication abortion. Contraception 2007;76:101-104 and Horning EL, et al. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. Contraception 2012;85:402-407.*
In these studies a mean age is provided, but a specific age range is not given. Please confirm whether the age range of study subjects includes adolescents < 17 years old and provide information about distribution of subjects by age (i.e., number of subjects at each year < 17).

For the articles listed above, provide additional information on adherence to the follow-up method comparing adolescents < 17 years and adults (≥17 years).

Please provide the requested information by close-of-business November 13, 2015.

Clinical Pharmacology Request:

Reference is made to the 74 day letter dated August 11, 2015 requesting the you to address the following two clinical pharmacology issues:

1. Address the effect of CYP3A4 inducers on the pharmacokinetics (PK) and efficacy of 200 mg mifepristone. This can be done by providing any published literature on the drug interaction between CYP3A4 inducers and mifepristone.

2. Provide the PK characteristics of a single dose of 200 mg mifepristone and address nonlinear PK in the range of available doses (200 to 600 mg).

In the response received on August 13, 2015, you submitted one published article (b) (4). However, rather than discussing the effect of CYP3A4 inducers on mifepristone, this article addresses the (b) (4) potential of mifepristone. **We request that you address the effect of CYP3A4 inducers on the PK and efficacy of 200 mg mifepristone.**

To address the PK characteristics of a single dose of 200 mg mifepristone, you submitted the list of conducted PK studies, including a PK study report of 200 mg mifepristone (Study 87/517 (b) (4) entitled “Bioequivalence study of 4 dosage forms of RU 38 486 administered orally to healthy male volunteers”). However, it is unclear if either or both of the two formulations of 200 mg mifepristone used in this study are bioequivalent to the currently approved formulation. **We request that you clarify the comparability of the formulations used in this study to the currently approved formulation. You should address the PK characteristics of a single 200 mg dose of the two-be-marketed formulation of mifepristone for labeling information.**

APPEARS THIS WAY ON ORIGINAL

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/s/

(b) (6)

10/30/2015

(b) (6)

From: (b) (6)
Sent: Monday, October 05, 2015 12:49 PM
To: (b) (6)
Subject: Information Request for supplement
Attachments: 20687s20ir10.5.15.doc

(b) (6)

Please find attached an information request for your pending supplement. Let me know if you have any questions.

Thanks,

(b)
(6)

We refer you to your efficacy supplement dated May 29, 2015. Please provide the additional information requested below by close of business on October 16, 2015.

1. In the Dosage and Administration section of your proposed label for Mifeprex, you propose (b) (4) In the subsection 2.4 entitled "Post-treatment Assessment: Day 7-14" you propose an additional dose of buccal misoprostol 800 mcg if termination has not occurred by the 7-14 day follow-up in women (b) (4)

Please address whether there are adequate data to support inclusion of such labeling and submit these data if available. If, based on available evidence, you elect to add to the proposed label that an additional dose of misoprostol may be taken if termination has not occurred by the 7-14 day follow-up in women (b) (4)

2. You propose to add misoprostol to the indication statement for Mifeprex such that the new indication will state: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through (b) (4) days gestation." We are aware of safety concerns regarding the risk of uterine rupture if misoprostol is administered in pregnant women beyond the eighth week (56 days) of pregnancy.

Please provide documentation (literature, adverse event reports) that addresses this potential risk between 56 (b) (4) days gestation.

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/s/

(b) (6)

10/05/2015



NDA 020687/S-020

**FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED**

Danco Laboratories, LLC
Attention: [REDACTED] (b) (6)
[REDACTED]
P.O. Box 4816
New York, NY 10185

Dear [REDACTED] (b) (6):

Please refer to your supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Mifeprex (mifepristone) Tablets.

We also refer to your amendments dated June 5 and July 17, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **March 29, 2016**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **February 28, 2016**.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Clinical Pharmacology

1. Address the effect of CYP3A4 inducers on the pharmacokinetics (PK) and efficacy of 200 mg mifepristone. This can be done by providing any published literature on the drug interaction between CYP3A4 inducers and mifepristone.
2. Provide the PK characteristics of a single dose of 200 mg mifepristone and address nonlinear PK in the range of available doses (200 to 600 mg).

Clinical

1. You provided an article (Gatter M, et al Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 201;91:269-273) describing a study that included women <18 years of age, (b) (4), (b) (6)
(b) (4), (b) (6)
2. The following articles from the medical literature appear to be relevant to the efficacy supplement. If you wish us to consider them, submit them for our review:
 - ACOG Committee Opinion: Increasing Access to Abortion. Number 613, November 2014.
 - Bracken H et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. *Contraception* 2014;89:181-186.
 - Cameron S et al. Can women determine the success of early medical termination of pregnancy themselves? *Contraception* 2015; 91:6-11.
 - Chen MJ and Creinin. Mifepristone with buccal misoprostol for medical abortion. *Obstet Gynecol* 2015 126 (1):1-10.
 - Chong E et al. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012;86 (3):251-256.
 - Cleland K et al. Significant Adverse Events and Outcomes After Medical Abortion. *Obstet Gynecol* 2013;121:166–71.
 - Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271–278.
 - Gallo MF et al. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006;74:36-41.
 - Ireland LD, Gatter and Chen. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015 126 (1):22-28.

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PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted studies with this application that included pediatric patients ≤ 17 years old. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call

(b) (6)

Sincerely,

{See appended electronic signature page}

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Center for Drug Evaluation and Research

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/s/

(b) (6)

08/11/2015

REQUEST FOR CONSULTATION

TO (Office/Division):
CDER- (b) (6) (b) (6)

FROM (Name, Office/Division, and Phone Number of Requestor):
(b) (6)
(b) (6)

DATE July 29, 2015	IND NO.	NDA NO. 20687/S-020	TYPE OF DOCUMENT Paper	DATE OF DOCUMENT May 29, 2015
NAME OF DRUG Mifeprex (mifepristone)	PRIORITY CONSIDERATION 10 month clock	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE February 1, 2015	

NAME OF FIRM: Danco Laboratories, LLC

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please see SharePoint link below for the proposed label for NDA 22687/S-020. The PDUFA Goal date for this efficacy supplement is March 29, 2016.

[http://sharepoint.fda.gov/orgs/CDER-\(b\) \(6\)/SitePages/Home.aspx?RootFolder=%2FForgs%2FCDER% \(b\) \(6\) %2FShared%20Documents%2FPending%20applications%20%28NDAs%5FBLAs%29%2FNDAs%2FNDAs%2020687s20&FolderCTID=0x012000794D24CB49BB2546AB3680561955B97C&View={3F634D63-6CD7-44DF-B2F5-0300E43F7710}](http://sharepoint.fda.gov/orgs/CDER-(b) (6)/SitePages/Home.aspx?RootFolder=%2FForgs%2FCDER% (b) (6) %2FShared%20Documents%2FPending%20applications%20%28NDAs%5FBLAs%29%2FNDAs%2FNDAs%2020687s20&FolderCTID=0x012000794D24CB49BB2546AB3680561955B97C&View={3F634D63-6CD7-44DF-B2F5-0300E43F7710})

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

APPEARS THIS WAY ON ORIGINAL

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/s/

(b) (6)

07/29/2015



NDA 020687/S-020

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Danco Laboratories, LLC
Attention: [REDACTED] (b) (6)
[REDACTED]
P.O. Box 4816
New York, NY 10185

Dear [REDACTED] (b) (6):

We have received your Supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 020687
SUPPLEMENT NUMBER: 020
PRODUCT NAME: Mifeprex (mifepristone) Tablets
DATE OF SUBMISSION: May 28, 2015
DATE OF RECEIPT: May 29, 2015

This supplemental application proposes to [REDACTED] (b) (4) dosing regimen.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 28, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be March 29, 2016.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 020687/S-020** submitted on May 28, 2015, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
[REDACTED] (b) (6)
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at [REDACTED] (b) (6).

Sincerely,

{See appended electronic signature page}

[REDACTED] (b) (6)
[REDACTED] (b) (6)
Center for Drug Evaluation and Research

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/s/

(b) (6)

06/11/2015



NDA 020687

MEETING MINUTES

Danco Laboratories, LLC
Attention: (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifeprex (mifepristone) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 29, 2015. The purpose of the meeting was to discuss a supplement to revise the dosing regimen and conditions of use for Mifeprex.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)
(b) (6)

Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-sNDA

Meeting Date and Time: January 29, 2015; 1:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 020687
Product Name: Mifeprex (mifepristone) Tablets
Indication: medical termination of intrauterine pregnancy through 49 days' pregnancy
Applicant Name: Danco Laboratories, LLC

FDA ATTENDEES

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Center for Drug Evaluation and Research

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SPONSOR ATTENDEES

(b) (6)

Philip Katz – Hogan Lovells

(b) (6)

BACKGROUND

Mifeprax was approved September 28, 2000 for medical termination of intrauterine pregnancy up to 49 days' gestation. The approved regimen is 600 mg Mifeprax orally, administered in a clinic, medical office or hospital (healthcare facility), followed by 400 mcg of misoprostol taken orally two days after mifepristone dosing, in the healthcare facility.

The Applicant is seeking guidance on a supplement to change the dosing regimen and conditions of the approved regimen. The Applicant would like to modify the regimen as follows:

- Extend the use of the product from 49 days' gestation to (b) (4) days' gestation
- Decrease the Mifeprax dose to 200 mg (from 600 mg)
- Change the interval between Mifeprax and misoprostol administration to a minimum of 24 hours up to two days later (from "two days" after Mifeprax)
- Increase the misoprostol dose to 800 mcg, with misoprostol to be administered buccally (from 400 mcg dosed orally)
- Administration of misoprostol at home (rather than in the healthcare facility)
- Required follow-up assessment (vs. 14 day follow-up visit)
- Additional dose of misoprostol if expulsion has not occurred by follow-up assessment

The Applicant would also like to change the labeled time to expulsion to 2-24 hours (from 4-24 hours). Further, the Applicant proposes to add a Warning to evaluate for ectopic pregnancy in any women who are found to be pregnant with an IUD in place.

In addition to the changes to the regimen for NDA 020687, the Applicant would like to discuss

(b) (4)

FDA sent Preliminary Comments to Danco Laboratories, LLC on January 28, 2015.

SPONSOR'S QUESTIONS AND DIVISION'S RESPONSES

Question 1: Does the FDA concur that the body of published literature, including approximately 17,800 women using the proposed (b) (4) regimen, is sufficient to support the addition of the proposed (b) (4) regimen?

FDA Response to Question 1:

The adequacy of the published literature will be a review issue. The Division agrees that using published literature, under a 505(b)(2) approach, could be an appropriate way to support an efficacy supplement for a different dosing regimen. Refer to **505(b)(2) REGULATORY PATHWAY**, below.

Discussion at the Meeting:

The Applicant noted that a paper to be published in Contraception by M. Gatter et al. about a study that evaluated the proposed new dosing regimen will bring the collective number of subjects treated with the regimen up to about 31,000.

Question 2: Does the FDA concur that this dosing regimen can be (b) (4)

FDA Response to Question 2:

The Applicant should explain why it proposes to (b) (4)

Discussion at the Meeting:

The Applicant explained that it (b) (4) The Division indicated that the acceptability of (b) (4) will be a review issue.

Question 3: The added language is intended to reflect (1) mifepristone is not approved for use on its own and is approved only for use with misoprostol; and (2) the published data demonstrate efficacy through (b) (4) days' gestation. Does the FDA agree with these additions?

Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 49 (b) (4) days' pregnancy gestation. ~~Patients taking Mifeprex must take 400 meg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time.~~

FDA Response to Question 3:

The Division agrees that Mifeprex is intended for use in combination with misoprostol.

The adequacy of the proposed clinical data to support efficacy through (b) (4) days' gestation will be a review issue. The Applicant is requested to provide safety and efficacy data stratified by week of gestation.

Discussion at the Meeting:

There was discussion of the implications of specifically referring to use with misoprostol in the indication statement for Mifeprex. The Applicant raised the possibility of changing the reference to "(b) (4)", (b) (4). FDA stated that the scientific and clinical accuracy of such a statement would have to be considered.

The Applicant noted that efficacy data stratified by gestational age in weeks would be provided, but that the publications typically have not reported safety by gestational week. Because serious adverse events are rare, the Applicant does not believe this will be a concern. The Division concurred.

Question 4: *The current PI contains data that Mifeprex alone results in complete abortions before administration of misoprostol in 5.3% to 6.3% of patients. More recent studies indicate that this rate is even lower, i.e., 1.4%. In light of this, and given that the revised PI would provide for the patient to take misoprostol at home, we believe it important for patients to complete the full regimen (i.e., Mifeprex and misoprostol) in all instances, in order to reduce as much as possible the risk of ongoing pregnancies. For that reason, we propose to delete the second sentence in the indication [see proposed language in Question 3], and add to the Dosage and Administration section the following statement:* (b) (4)

adjusted for details of the proposed regimen. Does the FDA agree with the proposed deletion?

FDA Response to Question 4:

With respect to the proposed new dose regimen, it appears that the above statement is in error and should instead state: “Patients taking Mifeprex must take 800 mcg of buccal misoprostol 24-48 hours after taking mifepristone.” Confirm whether this is the intended statement. The adequacy of the data to support the revised labeling for the new proposed dose regimen will be a review issue.

The proposed statement appears reasonable with respect to the currently labeled dose regimen but will be considered further during the review cycle; see response to Question 2.

Discussion at the Meeting:

The Applicant agreed with the Division’s correction and that a (b) (4)

Question 5: *Does the FDA concur that this important information for healthcare providers and patients [changing labeled “time to begin expulsion” from 4-24 hours to 2-24 hours after misoprostol] should be revised as Danco proposes?*

FDA Response to Question 5:

The adequacy of the proposed clinical data to support revision of the time to expulsion will be a review issue.

Discussion at the Meeting:

The Applicant clarified that this revision is important because it allows women better information on what to expect following misoprostol administration, which will allow them to adjust plans regarding travel, work, child care, etc.

Question 6: *Does the FDA concur that the term “ (b) (4) can be used throughout the label in place of all other terms?*

FDA Response to Question 6:

The impact of such a change on all aspects of labeling, including the Prescriber’s Agreement and REMS, must be carefully considered. Further discussion of this topic will be needed.

Discussion at the Meeting:

The Applicant noted that state laws govern who is allowed to prescribe; by changing the term to “(b) (4)” FDA would not be specifying particular types of healthcare providers, which may be at odds with what state law allows. While the REMS will need to be changed with the approval of a new dosing regimen, the term “physician” is not used currently in the REMS document; it uses either “healthcare provider” or “prescriber.” FDA will discuss this issue further internally and during the review cycle when the supplement is submitted.

Question 7: *Does the FDA concur with the proposed deletion? [“under Federal law” to be deleted from two places in the Prescriber’s Agreement]*

FDA Response to Question 7:

Further discussion of this topic will be needed. FDA would like to have a better understanding of Danco’s concerns regarding this language.

Discussion at the Meeting:

The Applicant acknowledged that the conditions of approval, such as the REMS, would constitute “Federal law.” However, it does not believe the two references to “Under Federal law...” in the Prescriber’s Agreement are necessary. FDA will discuss this issue further internally and during the review cycle when the supplement comes in.

Question 8: *Does the FDA agree that* (b) (4)

FDA Response to Question 8:

FDA has the following comments about (b) (4)

█ [Redacted]

█ [Redacted]

█ [Redacted]

(b) (4)

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Discussion at the Meeting:

(b) (4)

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OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the (b) (6) (b) (6) (b) (6) (b) (6). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Discussion at the Meeting:

The Applicant will research the issue of PREA requirements, but agrees they would apply to both the Mifeprex efficacy supplement and (b) (4). The Division noted that, although not directly applicable, sponsors of contraceptive products have typically addressed PREA by requesting a waiver of studies in premenarcheal females, and by extrapolating adult data to postmenarcheal females. The Applicant was advised to be familiar with language in PREA regarding extrapolation. The Division suggested that the Applicant could review information about extrapolation from adult data in the public record for Plan B.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Discussion at the Meeting:

The Division advised that proposed labeling also would be required to comply with the recently finalized Pregnancy and Lactation Labeling Rule (PLLR). The Applicant was referred to the

December 2014 draft guidance *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm425398.pdf>

MANUFACTURING FACILITIES [REDACTED] (b) (4)

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505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION

[Identify any issues that remain open at the end of the meeting and require further discussion at a later date. If none exist, please indicate that there were no issues requiring further discussion]

ACTION ITEMS

- Minutes to Applicant within 30 days.

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

/s/

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02/26/2015