[redacted]

The Danco Group

August 18, 1999

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8/21/99

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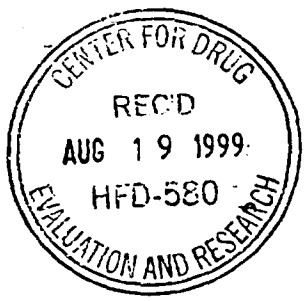


Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 033 - Remaining Responses to "FDA Approvable Letter of September 18, 1996." **Final Submission**

Dear [redacted]

This Amendment 033 responds to the Approvable Letter points #1 on "Distribution", #8 on the final technical point on "Substance", #12 on "Phase 4 Commitments" and #19 on "Promotion". All the other points (15) from the Approvable Letter have been responded to previously.

For your easy reference, the attached Summary of Approvable Letter Points and Related Responses provides amendment # and date of submission for responses to each point from the Approvable Letter. We have additionally included separate sections for points 1 to 19 which list the FDA question or comment as well as the amendment number and date for the response to the FDA.

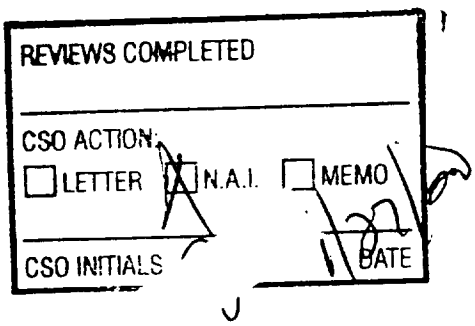
With the filing of Amendment 033, all the points raised in the Approvable Letter have been satisfactorily responded to and the NDA is now complete and ready for your final review.

If during the review process you have any questions on our responses, please don't hesitate to contact me.

Sincerely,

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council



APPEARS THIS WAY
ON ORIGINAL

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

[redacted] **to Robbins, Ph.D., Ann (September 18, 1996)**

Point #1

COMMENT: "Clinical
Please submit a comprehensive description of the proposed distribution system"

RESPONSE: The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.
- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.
- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.
- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:

  - The ability to accurately confirm the duration of pregnancy
  - The ability to determine blood Rh factor
  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgement from the patient that they have been provided with the product label, that they have

- read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.
- Place the dose # on the acknowledgement and in the patient record.
- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.
- Fill out and return AE (Adverse Event) cards to distributor,
- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.
- Provide the distributor with as much information as possible if there is an ongoing pregnancy following completion of the treatment procedure and this pregnancy is not terminated.

In addition, the toll free telephone number will enable providers to request training materials and information, and speak to an experienced medical consultant about either a non-emergency patient issue or an urgent medical problem or possible complication. Through a separate routing on the toll free telephone number, patients will have access to general information about the product, a provider location near them and web page addresses for more information.

The final distribution system will be more fully developed in the next few months but will always attempt to ensure that the drug is only supplied to qualified physicians/hospitals who register with the distributor, that the patient is given access to the product label and the patient information and reads and signs the acknowledgement, that the product # is placed on the acknowledgement in the patient's file and that the anonymity of the patient is maintained.

Market launch will not occur until the distribution system is finalized and there are adequate systems in place to track shipment and use. We would be happy to discuss this distribution system in detail with the FDA if there are any specific issues the Agency wants addressed.

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

(September 18, 1996)

Point #8

COMMENT: "Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure."

RESPONSE: We are mindful of our Phase 4 commitments as outlined in the Population Council's letter to FDA dated September 16, 1996. We plan to discuss in more detail and develop a consensus with the FDA post-NDA approval.

Attachments: Population Council September 16, 1996 letter

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. [redacted] **Robbins, Ph.D., Ann (September 18, 1996)**

Point #19

COMMENT: "In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products, and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857"

RESPONSE: We are in the process of developing the introductory promotional materials that we plan to use for the product and will submit the required three copies (in draft or mock-up form) together with the package insert, as soon as the promotional materials are ready.

APPEARS THIS WAY
ON ORIGINAL

e Population Council
ter for
medical Research

1230 York Avenue
New York, New York 10021
Cable: Popblomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

VIA FEDEX

September 16, 1996

Division of Reproductive and Urologic
Drug Products (HFD-580)
Center for Drug and Evaluation Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets/Amendment 004

Dear ———

We refer to our above New Drug Application for mifepristone which was submitted on March 14, 1996. We wish to amend our application with the following information:

1. A summary of the severe adverse events, (defined as any event that resulted in the generation of a Medwatch report to the FDA), that occurred during The Population Council's U.S. trial on the use of mifepristone and misoprostol for termination of early pregnancy is attached in Appendix 1. A comparison of the frequency of these events in the U.S. trial and those reported in the French pivotal studies included in the NDA is also provided. This information was reported at the July 19, 1996 meeting of the Reproductive Health Drugs Advisory Committee. When the analysis of the safety and efficacy data from the U.S. clinical trial is complete, a full report will be submitted to the NDA.

2. The letter from ——— of August 22, 1996 lists six Phase 4 studies recommended by members of the Reproductive Health Drugs Advisory committee at the meeting held on July 19, 1996. The Population Council concurs with the desire to gain additional information on the initial use of the product after approval and our response to these proposed studies is presented in Appendix 2.

e Population Council

Please contact me if there is any further information required by your division.

Sincerely,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yho

APPEARS THIS WAY
ON ORIGINAL

Appendix 2

This appendix sets forth the response of The Population Council, Inc. (The "Council") to the FDA's letter of August 22, 1996, a copy of which is enclosed. The numbered paragraphs below correspond to the six items in the FDA's letter.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

2. Although the Council cannot commit to a study that follows *all* women who have surgical abortions following failed mifepristone abortions, we would propose to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time, for instance six months or one year. In such an investigation, we would classify women undergoing medical abortion according to whether they 1) completed their abortions successfully; 2) had a failed medical abortion and required a surgical abortion; 3) required surgical intervention for other reasons; or 4) were lost to follow-up.

We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifepristone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. As stated in our response to proposed study #2 above, we are willing to supply treatment failure data from a sample of providers for a mutually agreeable period of time, for instance six months or one year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those

who smoke will be collected in the sample of women we have agreed to study, as described in item Numbers 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated.

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #1

COMMENT: "Clinical
Please submit a comprehensive description of the proposed distribution system"

RESPONSE: Submitted as part of Amendment 033 dated August 18, 1999

APPEARS THIS WAY
ON ORIGINAL

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, Robbins, Ph.D., Ann (September 18, 1996)

Point #2

COMMENT: "Chemistry, Manufacturing and Controls

Drug Substance:

1. [redacted] cannot be considered a starting material for the synthesis of mifepristone. It is not a commercially available material, its structural characteristics are not described in the literature, and its synthesis is described only in the patent literature.

   Full step-by-step details of the synthesis of [redacted] should be provided from simpler, commercially available starting materials that have been well characterized in the literature. Three of the five stereogenic centers in mifepristone are already established in [redacted] and, consequently, assurance that undesired diastereomers are adequately controlled is necessary. Three potential impurities in [redacted] have been identified; however, it is not obvious why the [redacted] has not been included in this list. A test for residual solvents is also necessary. Since this is an optically active compound, enantiomeric purity, using a method that will distinguish one enantiomer from another, should be determined or evidence provided that the undesirable enantiomer is not carried through the synthesis to give products that contaminate the drug substance."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999 and as part of Amendment 030 dated July 22, 1999.

APPEARS THIS
ON ORIG

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #3

COMMENT: "Chemistry, Manufacturing and Controls

Drug Substance:

The assay method of [redacted] should be specified and a Certificate of Analysis from the supplier submitted."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999.

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #4

COMMENT: "Chemistry, Manufacturing and Controls

Drug Substance:

An identification test for [redacted] should be performed."

RESPONSE: Submitted as Amendment 029 dated July 14, 1999.

APPEARS THIS WAY
ON ORIGINAL

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #5

COMMENT: "Drug Product:

An identification test that is specific for mifepristone should be performed; identification solely by [redacted] is generally not sufficient. Uniformity of dosage units by weight variation should be determined in accordance with USP23 <905>."

RESPONSE: Submitted as part of Amendment 030 dated July 22, 1999.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #6

COMMENT: "Biopharmaceutics

To support the rationale for using the stated dissolution medium and volume plus the selected [redacted] the proposed dissolution method, please provide the following information:

1. pH solubility data for mifepristone;

2. Sink condition information at 37°C for various media;

3. Tablet dissolution profiles (including raw data and mean data) in various media (i.e., simulated gastric fluid and simulated intestinal fluid, at a range of pH's representative of physiological conditions) that provide adequate sink conditions with appropriate sampling times to characterize the profile; and

4. Raw data and profiles at different paddle rotation speeds [redacted] in the dissolution media cited above."

RESPONSE: Submitted as Amendment 030 dated July 22, 1999.

APPEARS THIS WAY ON ORIGINAL

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #7

COMMENT: "Physician Labeling

General Comments
Black Box Warning
Description Section
Clinical Pharmacology Section
Indications and Usage Section
Contraindications Section
Warnings Section
Precautions Section
- General Subsection
- Drug Interactions Subsection
- Pregnancy – Teratogenic Effects Subsection
- Nursing Mothers Subsection
- Pediatric Use Subsection

Adverse Reactions Section
How Supplied Section"

RESPONSE: Submitted as Amendment 027 dated June 25, 1999

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter. Robbins, Ph.D., Ann (September 18, 1996)

Point #8

COMMENT: "Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system.

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

3. To assess the long-term effects of multiple use of the regimen.

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.

6. To ascertain the effect of the regimen on children born after treatment failure."

RESPONSE: Submitted as part of Amendment 033 dated August 18, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted], Robbins, Ph.D., Ann (September 18, 1996)

Point #9

COMMENT: "Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug: Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug product.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, (3) other dose levels, etc."

RESPONSE: Submitted as Amendment 031 dated August 3, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted], Robbins, Ph.D., Ann (September 18, 1996)

Point #10

COMMENT: "Clinical:

> We remind you of your commitment to submit full study reports of the U.S. trials promptly after their completion. We anticipate that you will revise your labeling to incorporate U.S. data at that time."

RESPONSE: Submitted as Amendment 024 dated June 3, 1999.

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #11

COMMENT: "Drug Substance:

1. The NMR spectrum of mifepristone does not display a horizontal chemical shift scale. Please provide a more legible reproduction. We recommend that a ^{13}C NMR of mifepristone be recorded to further confirm the structure."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #12

COMMENT: "Drug Substance:

2. We recommend that an assay method for [redacted] be developed and submitted along with appropriate proposed limits."

RESPONSE: Submitted as part of Amendment 033 dated August 18, 1999

APPEARS THIS WAY
ON ORIGINAL

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #13

COMMENT: "Drug Substance:

3. We recommend that a specification for polymorphic form, with suitable acceptance criteria, be included in the Regulatory Specifications for the drug substance."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, Robbins, Ph.D., Ann (September 18, 1996)

Point #14

COMMENT: "Drug Substance:

4. The specification limit for residual based on the batch data."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999

APPEARS THIS WAY
ON ORIGINAL

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #15

COMMENT: "Drug Substance:

5. The degradation product observed at the origin (Rf 0) in the thin-layer chromatograms should be structurally identified, if possible. Regarding drug substance stability data, we recommend:

   a. Actual assay and impurity content values be reported rather than values relative to those obtained for samples stored at refrigerator temperature, and

   b. The amounts of the degradation product, [redacted], be determined, not just the total impurity content."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999

APPEARS THIS WAY
ON ORIGINAL

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #16

COMMENT: "Drug Substance:

6. Please clarify whether the specifications for hardness of mifepristone tablets in the stability studies are the same as those for the in-process controls. An explanation should be given for the failure of batch RG 21236-44 to meet these specifications. We recommend that a more sensitive method be developed for quantifying the amount of degradation and numerical values reported rather than the qualitative statements like "no change" or "slight change". Assay values should be reported as percent label claim and not as a percentage of initial value. Lastly, the integrity of the polymorphic form of mifepristone used in the formulation should be monitored in the drug product stability studies."

RESPONSE: Submitted as Amendment 030 dated July 22, 1999.

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #17

COMMENT: "7. Please clarify whether the method of preparation of the reference standard for mifepristone is the same as described for batch manufacture and if there were additional purification steps. Please provide a Certificate of Analysis for the reference standard."

RESPONSE: Submitted as part of Amendment 029 dated July 14, 1999

August, 1999

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, [redacted] Robbins, Ph.D., Ann (September 18, 1996)

Point #18

COMMENT: "Drug Product:

Please provide the composition of the [redacted] used in the manufacture of the blister packs as well as a Certificate of Analysis from the supplier of the PVCA sheets. The polymers should meet the requirements of the relevant sections of 21 CFR Part 177. The composition of the heat-sealable varnish and the varnish applied to the outer surface of the aluminum foil should be stated or a DMF reference submitted, if available."

RESPONSE: Submitted as Amendment 030 dated July 22, 1999.

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

F.D.A. Letter, 1996) **Robbins, Ph.D., Ann (September 18,**

Point #19

COMMENT: "In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Reproductive and Urologic Drug Products, and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857"

RESPONSE: Submitted as part of Amendment 033 dated August 18, 1999

APPEARS THIS WAY
ON ORIGINAL

Population Council

NDA 20-687

Shelley Clark, Ph.D.
Staff Program Associate

Phone: 212-339-0617
Email: sclark@popcouncil.org

ORIG AMENDMENT

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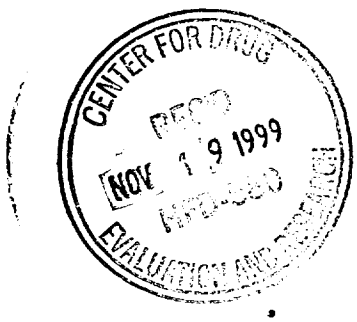
8 September 1999



Food and Drug Administration
Div. of Reproductive and Urologic Drug Products
Room ——— HFD-580
Center for Drug Eval. and Res.
5600 Fishers Lane
Rockville, Maryland 20857

Dear ———

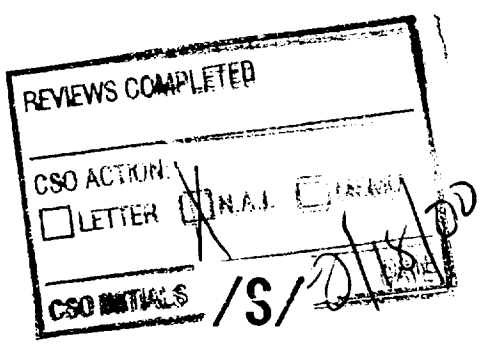
As per our phone conversation on September 2, 1999, I am sending you an updated electronic and hard copy of the label for the U.S. Please note we have added a place for the "'Tradename' package ID number" at the end of the document for drug tracking and control purposes.

Enclosed please also find the most recent labels in our files from France, U.K. and Sweden. We will continue to look for the current labels from these countries since some of our copies of these labels may be outdated or incomplete. For example, while we have the data sheet and patient information leaflet from the U.K., we appear to be missing some pages from their official label. Also a section of the French label was not translated into English (as marked). We will send you the most recent labels as soon as we locate them. In the meantime, if you need any additional information on the U.S. or foreign labels, please feel free to contact me via phone at 212-339-0617 or via e-mail at sclark@popcouncil.org.

Sincerely,

Shelley Clark

Shelley Clark, Ph.D.



cc: Sandra Arnold, Population Council

enclosures: French label
Translation of French label
Data sheet for U.K.
Patient information leaflet for U.K.
U.K. label (incomplete)
Swedish label
Updated U.S. label

Appendix 2

This appendix sets forth the response of The Population Council, Inc. (The "Council") to the FDA's letter of August 22, 1996, a copy of which is enclosed. The numbered paragraphs below correspond to the six items in the FDA's letter.

1. The Council recognizes the need for additional information about our proposed distribution and credentialing system and the necessity for making certain that it is designed to result in safe and efficacious abortions for women and in properly controlled access to the product. We will provide the FDA with a detailed product distribution and provider credentialing plan that describes our own monitoring indicators, and we would welcome additional discussion with the Agency at that time. We intend to monitor the distribution and credentialing system but we do not believe that the frequency of post-surgical complications will necessarily be a meaningful indicator of its effectiveness.

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We are not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing this, as it could violate women's privacy.

3. A prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades. However, the Council has been informed that central registries of mifepristone users exist in Europe. We will examine these data sources to determine what can be learned about multiple use. In addition, in future studies of the regimen carried out by the Council in the U.S., we will attempt to develop a cohort of women who report more than one use of the regimen and agree to be followed.

4. As stated in our response to proposed study #2 above, we are willing to supply treatment failure data from a sample of providers for a mutually agreeable period of time, for instance six months or one year, bearing in mind that such data will not include women lost to follow-up.

5. The Council agrees that it is desirable to have additional information on users of the regimen who are under age 18, or over age 35 or who are smokers. From the French and United States clinical trials, we do have some data on women who were more than 35 years old and on women who smoked. The French trials also included some subjects who were under 18 years of age. We will submit an analysis of our safety and efficacy data on these subgroups. In addition, data on women under 18 or over 35 years of age and those

who smoke will be collected in the sample of women we have agreed to study, as described in item Numbers 2 and 4 above.

6. Since live births are extraordinarily rare as outcomes of treatment with mifepristone (e.g. approximately 19 out of more than 250,000 in the French database) this issue is best approached by reporting through providers who utilize the regimen. We will instruct our distributor to include materials for providers that ask them to report to the distributor any treatment failure in which the woman decides to continue her pregnancy. The provider will ascertain which of these women agree to be followed to document the health of any children born of such pregnancies. In addition, any spontaneous reports of live births of children exposed to mifepristone *in utero* will be investigated.

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

noted
11/30/99

November 29, 1999

ORIG AMENDMENT
BM

VIA FEDERAL EXPRESS

Division of Reproductive and Urologic Drug
Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets

Dear

Enclosed please find answers to the remaining questions raised by We have now answered all of , questions.

In reference to our first set of answers to questions we would like to clarify one point in our letter dated October 5, 1999. With regard to the answer to the first question, the safety information on the U.S. Trials was actually presented by Dr. Wayne Bardin instead of Dr. Ann Robbins at the Advisory Committee Meeting. Also, this information presented on the U.S. Trials was obtained from the MedWatch Forms which had been previously submitted to the FDA during the Trials as required. This information presented did not represent any analysis of the data base.

Please let us know if you need any additional information.

Very truly yours,

Sandra Arnold

Enclosures

cc: Dr. Shelly Clark

Dr. Frederick Schmidt
Dr. Irving Spitz
Dr. Beverly Winikoff

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

1. Question:

In our label, we say that time of expulsion is unknown for 122 patients, 14.8%. In the NDA tables, p.30, vol. 8.21, all expulsions are accounted for. Which is correct?

Answer:

The information provided in NDA Table 5.1 (page 30, Amendment 024, Vol. 21, June 3, 1999), entitled "Time to Occurrence of Complete Abortion", accounts for the occurrence of all expulsions in the study. However, this table does not provide the precise or actual timing of all of the expulsions. In Table 1b of our proposed labeling of September 8, 1999, for group 1, all of the expulsions are also accounted for, but for 122 of the expulsions the precise timing of the expulsion is unknown. Furthermore, these same data are presented in IND Serial No. 185, May 5, 1997, Table 7 (page 30) entitled "Expulsion Time". In conclusion, both the NDA Table 5.1 and Table 1b in our proposed labeling are correct.

2. Question:

In Volume 8.21, Amendment 24, Table 4.1, p. 27, it states that in group 1, 13 patients required medical intervention. In table 9.2, p. 168, it states that in group 1, 26 patients had medical interventions. What accounts for the difference?

Answer:

Table 4.1 (page 27, Amendment 024, Vol. 21, June 3, 1999) entitled "Treatment Outcome by Gestational Age" presents a summary of the "Total Successes" and "Total Failures" for each of the three (3) gestational age groups. Sixty-five patients in group 1 were classified as "Total Failures" and required surgical intervention. Thirteen (13) of these 65 patients had a surgical termination performed for medical indications and were referred to as Failures treated by "Medical Intervention". Medical intervention was performed at anytime during the course of the study at the discretion of the physician. Ten (10) of the thirteen patients, in group 1, who had a medical intervention were for bleeding reasons, one (1) for bleeding/endometritis, one (1) for psychotic/depression and one (1) for anemia and difficult physical examination because of fibroids.

Table 9.2 (page 168, Amendment 024, Vol. 21, June 3, 1999) entitled "Treatment for Bleeding" accounts for only those medical interventions performed for bleeding reasons. This differs from the above referenced Table 4.1 which provides for medical interventions for any medical reason. In Table 9.2 there are 26 subjects in group 1 who had a medical intervention for bleeding. Medical interventions included D & C, hormonal therapy and manual or electric vacuum aspiration. In addition, there were 17 patients in group 1 who received methergine treatment for bleeding.

Appendix A.1, Table 18, "Bleeding Status, Patients Present at Visit 3" provides a Safety Data Listing of all medical interventions required to stop bleeding and includes the specific method used for medical intervention. This data listing is presented separately for Protocol 166A (Table 18, Vol. 4, pages 298-332) and for Protocol 166B (Table 18, Vol. 14, pages 12-61).

In conclusion, Table 4.1 refers to method failures that required surgical termination, for any medical indication as determined by the physician; whereas, Table 9.2 summarizes medical interventions performed for bleeding reasons only whether the method was a success or a failure.

3. Question:

In table 4.2, p. 140, it states that 135 patients had uterine hemorrhage with misoprostol or with the combination of mifepristone and misoprostol. In table 4.1, p. 119, it states that 13 patients had uterine hemorrhage with mifepristone alone. These total 148. In our letter dated October 5, we cite 9 cases of uterine hemorrhage related to mifepristone and 127 cases related to misoprostol; this totals 136. What accounts for the difference?

Answer:

Table 4.2 (p.140, Amendment 024, Vol. 21, June 3, 1999) presents the adverse events, by body system, that were possibly or probably related to misoprostol or the combination of mifepristone and misoprostol. A total of 135 subjects had uterine hemorrhage as an adverse event. Some of these 135 patients had uterine hemorrhage as an adverse event on more than one occasion. Thus there were a total 152 adverse events for uterine hemorrhage. A total of 127 of the 152 adverse events for uterine hemorrhage, all groups, were judged to be severe.

Table 4.1 (p.119) shows the adverse events possibly or probably related to mifepristone alone. A total of 13 subjects had uterine hemorrhage as an adverse event. One of the 13 subjects had uterine hemorrhage as an adverse event on two occasions. Thus there were a total of 14 adverse events for uterine hemorrhage. A total of 9 of the 14 adverse events for uterine hemorrhage were judged to be severe.

In our October 5, 1999 letter we cite 9 cases of severe uterine hemorrhage related to mifepristone. This is in agreement with Table 4.1 above. Similarly we state that there are 127 cases of severe uterine hemorrhage related to misoprostol or the combination of mifepristone and misoprostol. This is as per Table 4.2.

4. Question:

The NDA states that 60 patients had surgery for medical indications. The IND states that 77 patients had surgery for excessive/prolonged bleeding. What happened to 17 reflected in the IND, but not in the NDA?

Answer:

In the U.S. Trials, 295 patients were classified as having failed medical abortions and required surgical intervention. Of these patients, 79 had ongoing pregnancies, 126 had incomplete abortions, 30 requested and had surgical termination, and the remaining 60 patients had surgical terminations performed for medical indications and were referred to as Failures treated by "Medical Intervention". (NDA 20-687, Amendment 024, June 3, 1999, Vol. 21, page 11 and Table 4.1 on page 27). As described above in our answer to the second question medical intervention was performed anytime during the course of the study at the discretion of the physician and for any medical reason. Thus, medical intervention comprises any medical reason including bleeding.

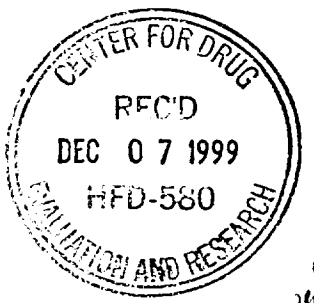
The 77 patients referred to in the IND includes those subjects who had surgery for excessive/prolonged bleeding and subjects with an incomplete abortion who also required surgical intervention for prolonged bleeding. Thus this group of subjects includes those patients who either had a method failure, success or an incomplete abortion.

ORIGINAL

The Danco Group ORIG AMENDMENT

BC

December 6, 1999



Reviewed. NAI.
2/19/00

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Form 483 for Substance Manufacturer, Product Manufacturer and Testing Laboratory

Dear

Pursuant to your request, I am enclosing Form 483 that was recently received for each of the Substance Manufacturer, the Product Manufacturer and the Testing Laboratory following their respective Pre-Approval Inspections (PAI). I am also enclosing the cover page indicating the transmittal date for each response.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely,

President and
Chief Executive Officer

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE 2/19/00

Enclosures

cc:

Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

December 2, 1999

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: October 25-28, 1999
Inspectional Observations (Form FDA 483): Corrective Action

Dear

On behalf of our principals, please find herewith enclosed, a response to the Inspectional Observations (Form FDA 483) issued at the conclusion of your recent inspection of their plant. Should you require any further information, please do not hesitate to contact the undersigned.

Thank you for your attention.

Sincerely,

/s/

President

Encl.

cc: Food and Drug Administration, Division of Manufacturing & Product Quality, HFD-322

Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food & Drug Administration, CDER, HFD-322 Div. of Manufacturing & Product Quality, FIT 7520 Standish Place Rockville, MD 20855, U.S.A. Phone: 001 301 594-0095 — FAX 001 301 594-2202	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Li Changfa	PERIOD OF INSPECTION 10/25-28/99	C. F. NUMBER 96-15606
TITLE OF INDIVIDUAL Chairman	TYPE ESTABLISHMENT INSPECTED API Manufacturer	
FIRM NAME ShangHai Hua Lian Pharmaceutical Co., Ltd. -- XinLian Pharmceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE *(Zip Code)* Shanghai 201419, China	CITY AND STATE *(Zip Code)* Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling f[illegible] was filling with waste solvent during this inspection. Other solvents such as [illegible] and [illegible] are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification.

2. For HPLC and GC analyses performed prior to September 1999, no formal system suitability was performed aside from the initial injection of reference standard.

3. No acceptance criteria have been established for calibration of the [illegible] analyzer although Q.C. approves the monthly calibration runs.

4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

Finished product testing:

a) The HPLC method used for release testing of the purified Mifepristone is not described in the CMC.

b) The specification for residual [illegible] in finished product on CMC page 168 is incorrectly reported.

c) The GC analysis for [illegible] on pages188-189 is incorrect. Flow rates and temperatures are incorrectly reported.

In- process/intermediate test methods:

a) For GC analyses of the "ANI" intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days.

b) There is limited resolution of the two major impurities from the main reactant in the HPLC method for in-processing monitoring of the [illegible]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* Compliance Officer	DATE ISSUED 10/28/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER U.S. Food & Drug Administration, CDER, HFD-322 Div. of Manufacturing & Product Quality, FIT 7520 Standish Place Rockville, MD 20855, U.S.A. Phone: 001 301 594-0095 — FAX 001 301 594-2202	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Li Changfa	PERIOD OF INSPECTION 10/25-28/99	C. F. NUMBER 96-15606
TITLE OF INDIVIDUAL Chairman	TYPE ESTABLISHMENT INSPECTED API Manufacturer	
FIRM NAME Shanghai Hua Lian Pharmaceutical Co., Ltd. -- XinLian Pharmceutical Factory	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 217 Ming Le Road	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE *(Zip Code)* Shanghai 201419, China	CITY AND STATE *(Zip Code)* Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

c) , CMC 143, section 2.1.3 states that the method is HPLC. Although a HPLC analysis is run, the former TLC method is being used for evaluation since the HPLC method is still under development.

d) The assay method for , CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by . Also, the TLC Related Substances method, section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution The cited dilutions are not the ones used. The wavelength for final reading under normal lighting is not mentioned.

Raw Material Testing:

a) [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* Compliance Officer	DATE ISSUED 10/28/99

November 22, 1999

RE: Pre-approval Inspection for NDA # 20 - 687

Dear

Please find our response to the FDA – 483 issued by
Investigator , Mr . We have sent a desk copy to

We are very grateful to you and especially to for his helpful advice and guidance durin
following the inspection.

Thanking you for your kind consideration.

Yours truly.

/S/

cc
Vice President, Manufacturing
Danco Laboratories Inc.

cc:

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone is

November 10, 1999

Re: 483 Observations issued to
NDA 20-687

Dear

In response to , recent PAI audit of our facility, and subsequent issuance of form 483 observations, , would like to offer for review, the following explanations and corrective actions.

Observation # 1

Technical transfer of all analytical methods to be used for release and stability testing of Mifepristone 200mg Tablets was not conducted. Further, two revisions of the protocol were generated for use, however neither was signed by the application holder as required. Technical transfer was incomplete in that only 3 of 9 test methods were addressed. There is no Quality Assurance review of the protocol prior to its implementation.

Response:

A technical transfer for quantitative methods was performed, documented in a repo[redacted]ded provided when requested. Physicochemical and compendial performance tests wer[redacted]ded in this report. The remaining six (6) methods were addressed in a summary of refe[redacted]ne innovator's method validation documents and a rationale for the treatment of phys[redacted]l and compendial performance tests. These were provided during the inspection (Attachment 1-1) as a supplement to the transfer report for the Assay, Related Substances and Dissolution Rate test methods for Mifepristone 200 mg Tablets.

Extensive conversations with the sponsor, prior to the study's initiation, concerning details of the study did in fact occur and were agreed upon. These details were provided in the quotations to the client, dated November 1998, and January 1999. Our current standard operating procedure, SP-CO030002, section 4.2.3, (Attachment 1-2) allows for the use of a sponsor signed quotation as a protocol, with any additional information formalizing the official protocol to be provided at a later date. The approved quotations for the transfer of release and stability methods, and the stability studies associated with the Mifepristone API and the Tablets, signed January 26, 1999, and April 6,7 1999 respectively, prior to the initiation of work, are provided for the official record. Attachment (1-3).

November 30, 1999

[redacted]

Re: Supplemental Documentation to response to 483 Observations issued to
NDA 20-687.

Dear Mr.

would like to provide the following supplemental documentation in support of our November 10th response to the 483 observations issued.

Observation #

1 & 8. , **"Issuing & Acceptance of Study Protocols".**
Amended to provide additional QA review of Protocols related to regulatory submissions as committed to in responses to Observation # 1 and Observation # 8.

2. **Validation of the Test Method for the HPLC Determination of Mifepristone in Mifepristone API for Danco, Inc.**
Performed as committed to in Observation # 2.

3. **Qualification of Mifipristone Reference Standard - Part 1.**
Performed as committed to in Observation # 3.

4. **'Analytical Services Division Laboratory Investigation Procedures".**
Amended to incorporate preliminary investigations, in addition to notebook documentation, when erratic data is generated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED

TO:

TITLE OF INDIVIDUAL

TYPE OF ESTABLISHMENT INSPECTED

NAME OF FIRM, BRANCH OR UNIT INSPECTED

STREET ADDRESS OF PREMISES INSPECTED

CITY AND STATE (Zip Code)

DURING THE INSPECTION OF YOUR FIRM WE OBSERVED:
NDA 20-687 Mifepristone 200mg Tablets

1. Technical transfer of all analytical methods to be used for release and stability testing of Mifepristone 200mg Tablets was not conducted. Further, two ~~versions~~ revisions 2nd 10/27/99 of the protocol were generated for use, however neither was signed by the application holder as required. Technical transfer was incomplete in that only ——— were addressed. There is no Quality Assurance review of the protocol prior to its implementation.

Item # 1 reported corrected but not verified.

2. The Method Transfer Protocol and Report for Mifepristone API lack data to support the transfer of all analytical methods to be employed for release and stability testing of the API as provided on the firms testing templates ——— methods were addressed). Further, there is no documented evidence that the data used for comparison in the transfer was obtained using the same methodology. Original analytical method validation packages were not available for review and the alternate assay by HPLC was not validated.

Correction of item #2 ~~and~~ promised by Nov. 10, 1999. 2nd 10/27/99

3. There is no reference standard available for testing of Mifepristone API or finished product manufactured by the supplier listed in the application (Shanghai Hualian). The Mifepristone reference standard, lot#4 V 1014 BJ, was manufactured by the innovator (Hoechst Marion Roussel) 10/94 and is currently used despite the new API supplier and new manufacturing facility.

No comment at this time.

4. On 3/15/99, chromatographic raw data files were voided for the testing of Mifepristone, API (manufactured by Shanghai Hualian), validation lot#s 990101, 990102, 990103 initiated 3/13/99, when standard and sample peaks did not elute at their expected retention times. Although it was theorized that the erroneous results were due to the temperature in the laboratory, the temperature recordings did not support that conclusion. There was no investigation report to invalidate the data. Further, the analytical method has not been validated to date and no corrective actions are in place to prevent future occurrences.

No comment at this time.

5. Electronic raw data files, generated for HPLC standard injections, are reused for bracketing sample injections in place of injecting the standard vial.

No comment at this time.

6. The audit trail available for the ——— software used for chromatographic data generated by the ——— systems has not been enabled. Multiple editions to a sequence can be created and reintegrations conducted by the analyst, however there is no mechanism for review of previously generated editions.

Correction of item #6 promised by Jan. 31, ~~1999~~ 2000. 2nd 10/27/99

SEE REVERSE OF THIS PAGE	EMPLOYEE (S) SIGNATURE	EMPLOYEE (S) NAME AND TITLE (Print or Type)	DATE ISSUED
	[S]	[S]	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED	PERIOD OF INSPECTION
TO:	
TITLE OF INDIVIDUAL	TYPE OF ESTABLISHMENT INSPECTED
	NAME OF FIRM, BRANCH OR UNIT INSPECTED: same
	STREET ADDRESS OF PREMISES INSPECTED: same
	CITY AND STATE (Zip Code): same

DURING THE INSPECTION OF YOUR FIRM WE OBSERVED:

7. Analytical laboratory temperature and stability chamber temperature and humidity data generated by the [redacted] were found to be unreliable from 7/99 through 9/99, according to firm officials. There is no documented investigation of the system failure or notification that employees were instructed to use the backup manual system of chart recorders to review stability chamber conditions.

No comment at this time.

8. Testing of Mifepristone API for the supplier listed in NDA 20-687 (Shanghai Hualain) was conducted without an approved Method Transfer Protocol. Data collection for the Mifepristone validation lot#s 990101, 990102, 990103 was initiated on 3/1/99. The protocol was approved by [redacted] on 3/8/99. Although the document provides for the applicant's approval signature, it is unsigned.

Correction of item #8 promised by Dec 8, 1999

Communication between the parent company (Danco), [redacted]) did not insure that incoming samples were identified to permit the use of the appropriate and validated test methods. For example:

a. Although firm officials stated that they had not received or tested Mifepristone API and finished tablets from an alternate manufacturer (Gideon Richter), testing was conducted for Gideon Richter API lot#s D62070 and D62080 and tablet lot#s 99002, 99003, 99004, and 99006 from 6/22/99 to 6/28/99. It is not known if the appropriate test methodologies were employed for this alternate supplier.

ok

b. Despite the different testing required for validation purposes (as evidenced by the testing template), firm officials could not identify the API or finished product validation batches. The contract manufacturer had to be contacted to obtain the information.

No comment at this time.

[redacted]

SEE REVERSE OF THIS PAGE	[redacted]	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	/S/	/S/	

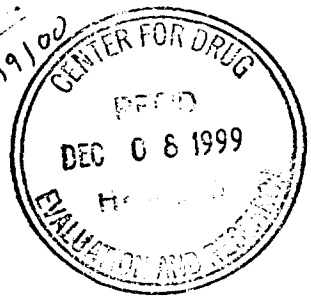
ORIGINAL

The Danco Group

[ORIG AMENDMENT BC]

December 7, 1999

Reviewed. See Chem Rev. #3. 2/19/00



Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 038 - Chemistry, Manufacturing and Controls (CMC) Section 2 for Drug Product: Amendment

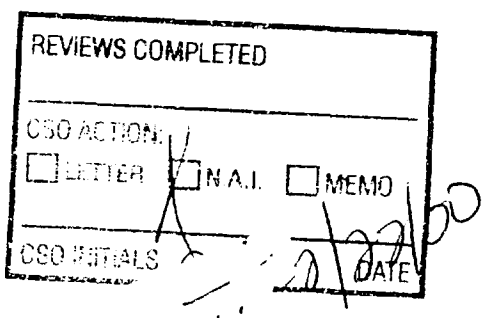
Dear

This Amendment #038 to the Drug Product CMC submission provides the revised formulation, tabletting and packaging master batch sheets (See attachments 1 & 2). These revisions reflect discussions with the FDA inspector during the Pre-Approval Inspection (PAI) of the Drug Product Manufacturer and the subsequent response filed with the regional office in November.

For your reference the master batch sheets appear in the original Drug Product CMC (Amendment #032) as pages 69-87 for the formulation and tabletting operation and pages 113-118 for the packaging operation. This Amendment #038 replaces these specific pages.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely,



President and
Chief Executive Officer

This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

/dns
Enclosure

cc:).
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	December 7, 1999
TELEPHONE NO. *(Include Area Code)* (212) 339-0663	**FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

1230 York Avenue
New York, NY 10021

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (Chemical Abstracts - (11β,17β)-11-[(4-Dimethylaminophenyl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of **all** manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 007649

FORMULATION AND TABLETTING BATCH RECORD

(REVISED)

The Danco Group

December 23, 1999

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

NC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Information Request Letter Dated December 14, 1999

Dear

As discussed yesterday, we are requesting a meeting with the FDA to discuss twelve of the items listed on the Information Request dated December 14, 1999. These are items 4, 5, 7, 8, 12, 16, 17, 19 and 25 from the Chemistry section and items 3, 10 and 11 from the Drug Product section. We are in the process of preparing responses to each item on this Request and therefore there may be some additions to this list. Other than representatives from the Population Council, Danco and Danco's FDA counsel, we will be bringing to the meeting Danco's Drug Substance and Drug Product consultants.

Our attendee list is as follows:

Sandra P. Arnold	Vice President –Corporate Affairs	Population Council
Frederick P. Schmidt	Scientist	Population Council
	President and Chief Executive Officer	The Danco Group
		The Danco Group
	FDA Counsel	
	FDA Counsel	

This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is ———

The day that is most suitable for all of the above participants is January 4. By meeting early, we can resolve any issues and respond in the earliest time frame. If this is not suitable for the FDA participants, we would have to look at the week of January 17.

On a separate point, we plan to submit a full distribution plan to the FDA by the middle of January and request an additional meeting to discuss this plan at the end of January or the beginning of February. Could you please also provide suggested dates for this meeting.

We look forward to your response with suggested meeting dates.

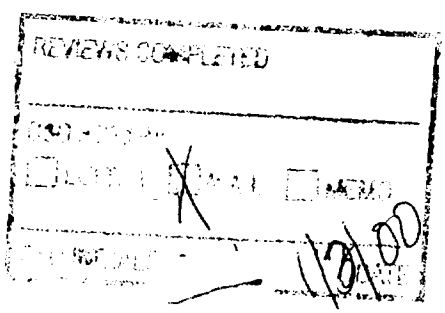
Sincerely,

Heather O'Neill

President and Chief Executive Officer

/dns

cc: – Danco Group
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council



The Danco Group

December 23, 1999

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Attention: Document Control Room 17B-20
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Frederick P. Schmidt	Scientist	Pop
	President and	The
	Chief Executive Officer	
	Vice President Manufacturing	The

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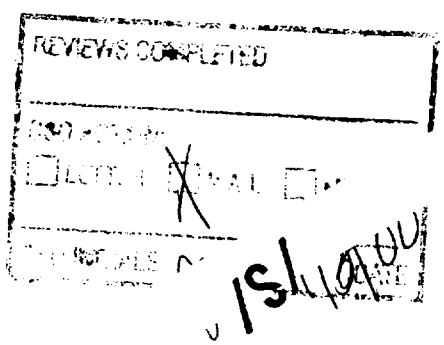
Sincerely,

President and Chief Executive Officer

/dns

cc: Danco Group
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

APPEARS THIS WAY
ON ORIGINAL



Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

October 25, 1999

VIA FEDERAL EXPRESS

Dear ———

This letter is in response to your inquiry concerning Roussel Uclaf's reasons for deciding not to market their product, mifepristone, originally known as RU-486, in the United States. As we believe you know, Roussel Uclaf decided in 1988 to withdraw mifepristone from the French and other markets in which it had been launched; this decision seemed to have been made on the basis of business pressures brought on the company by various constituencies in France and elsewhere in Europe. However, when the decision was announced, the French government took action to force Roussel Uclaf to continue to produce and market the product, stating that mifepristone was the moral property of French women. Roussel Uclaf reluctantly resumed providing the drug.

In the United States, there was considerable interest in the compound from reproductive rights activists and women's groups, and pressure was put on Roussel to market the product here. However, Roussel was unwilling to bring the drug into the United States, despite the fact that it held a US patent on it. Roussel, and its successor company Hoechst Marion Roussel (HMR), have for many years publicly expressed an extremely elevated level of fear as to the consequences for them of being identified as involved with mifepristone in the United States.

These concerns extend back to 1989 when clinical trials in California had to be stopped at the request of the company. They cited fear of public reaction that would be harmful to their interests. On many occasions Roussel (and subsequently HMR) executives expressed a very strong fear of adverse consequences if they were involved in bringing this product to the United States market. There is no question that this very high level of fear prompted many actions over a period extending across several years.

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

In January 1993, the just-elected President Clinton stated that bringing mifepristone to the United States was a priority. In follow-up, in February and March 1993, Donna Shalala, the Secretary of Health and Human Services, and David Kessler, then head of the Food and Drug Administration, communicated with Roussel executives to ask them to bring the product to the United States. Roussel consistently refused to be directly involved in this manner, citing commercial and personal risk, as well as the prevalence of litigation in the U. S. as their reasons. Roussel announced in April 1993 that they would instead transfer U.S. patent rights to the Population Council; the Council would conduct clinical trials, file the New Drug Application, and arrange for the manufacture and distribution of mifepristone in the United States.

More than 14 months of negotiations among the Council, Roussel and others were needed to find the administrative and insurance arrangements that would allay Roussel's concerns. Over 20 meetings involving the principals, scientists, and counsel were held with Roussel, Health and Human Services, and the Food and Drug Administration in New York, Paris, and Washington, D.C. Roussel's demands, as communicated to all parties involved, were directly related to their concerns regarding boycott, violence inflicted on their staff and facilities, and litigation, and included demands for indemnification from prosecution and/or harassment to be offered by the U. S. government.

It was not until May 1995 that the patent transfer was concluded. Roussel tried strenuously to have the U. S. administration extend the anti abortion-violence bill to cover all those economically or functionally associated with abortion provision. Roussel did not succeed, but these matters delayed the transfer by many months.

Since the transfer of the patent was made to the Council at no cost, and since cost was never discussed, it is absolutely clear that those 14 months of negotiations with the Population Council and others were focussed on meeting the concerns and fears of Roussel. These concerns did not abate even though they were not to be involved directly in bringing the product to the U. S. market. It was their view -- a view buttressed by the disorder and disruption at U. S. abortion clinics -- that the level of violence and animosity created around this issue would be such as to harm their interests. Repeatedly in this time, there were expressions of fear of injury to plant and personnel, boycott, repercussions on other products, and litigation.

After the patent transfer, Roussel/HMR fears continued to manifest themselves in their policies. In April 1998, HMR very speedily divested itself of all remaining rights to mifepristone, giving these to Exelgyn, a French company formed by Edouard Sakiz, the former CEO of Roussel. The Council was told that the reason for this very abrupt divestiture was that certain customers had threatened to withhold major purchases from the company as long as it was still linked to mifepristone in any fashion.

There is no question that continuing, pervasive fear of commercial, civil and physical violence and harm was a motivating factor throughout for these companies. This was expressed to us on many

occasions, delayed negotiation for many months, and continued to be brought forward as the underlying rationale for most of their policy positions.

We have attached a copy of a recent article from the *Toronto Sun* that discusses many of these issues.

Very truly yours,

Sandra Arnold

Sandra P. Arnold

Margaret Catley-Carlson

Oct 5/99

Enclosure

APPEARS THIS WAY
ON ORIGINAL

The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 039 - Mifeprex® – Distribution Plan

Dear

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

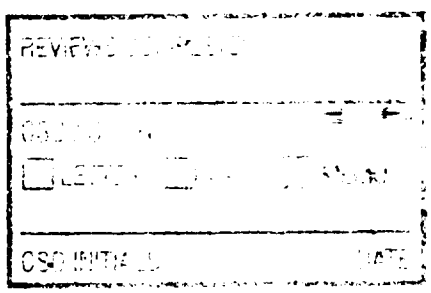
Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.



/dns
Enclosure

cc:

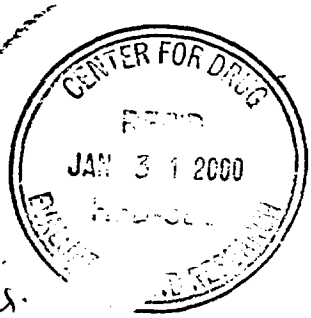
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

ORIGINAL

The Danco Group

January 28, 2000 ORIG AMENDMENT

BC



Reviewed. See Chem. Rev. #4. 2/19/00

Division of Reproductive and
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Attention: Document Control Room 17B-20
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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Amendment 040 - Chemistry, Manufacturing and Controls (CMC) Response to Information Request Letter of December 14, 1999

Dear

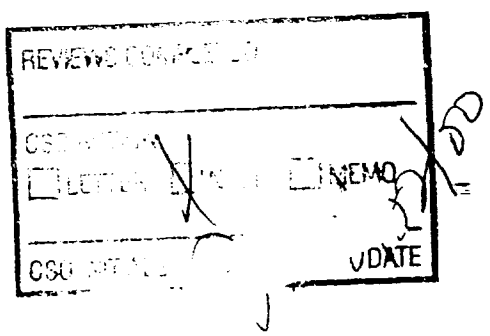
This Amendment 040 to the subject NDA provides complete responses to the Information Request Letter of December 14, 1999 sent to us by the FDA. In addition, this response provides the HuaLian Environmental Impact Statement.

Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely.

/S/

President and
Chief Executive Officer



/dns
Enclosures
cc:

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Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

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The Danco Group

January 28, 2000

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Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP
NC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

Dear

I am enclosing 2 additional copies of the Distribution Plan for Mifeprex®, which was originally submitted to the FDA as Amendment 039 dated January 21, 2000.

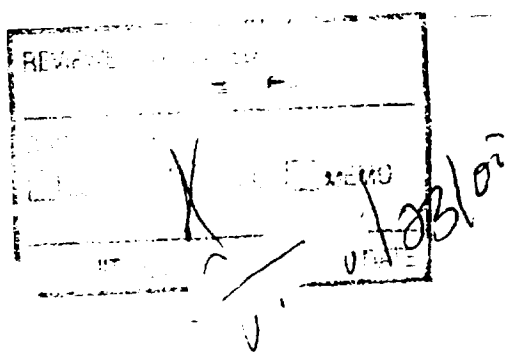
Sincerely

/S/

President and Chief Executive Officer

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council



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Food and Drug Administration
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Rockville, MD 20857

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President and Chief Executive Officer

/dns
Enclosure

cc:

Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

ENVIRONMENT ASSESSMENT FOR DRUG PRODUCT

Environment Assessment

1. Introduction

The environment assessment section of this NDA supplement is written in accordance to 21 CFR 25.31a(a) and The Guidance for submission of Environmental Assessment of Human Drug and Biologics Applications (FDA, 1999). The purpose of the EA is to supply information that will allow the Food and Drug Administration (FDA) to implement the provisions of the National Environment Policy Act of 1969 (NEPA). NEPA requires the FDA to identify actions that may significantly affect the quality of the human environment (21 CFR 25.1 (b)(1).

The Mifepristone drug product will be manufactured, packaged and labeled [redacted]. All drug product manufacturing, labeling and packaging will occur in full compliance with all applicable [redacted] regulations. Any potential for release of the drug substance directly to the environment normally could occur only through patient use and subsequent elimination.

The calculated expected introduction concentration (EIC) of the drug substance from patient use, based on the estimated annual production weight during the fifth year following NDA approval, and assuming no metabolism, depletion, or dilution, and uniform distribution, is [redacted]. Since the EIC value for the use of Mifepristone is less than one part per billion, Tier 0 criteria (from the 1999 FDA EA guidance) are met. Therefore, no formal environment assessment section is being submitted for this application. The EIC values are calculated in the next section.

The other components of the drug product are in common and constant use as excipients in many medicinal drugs and has been so for many years. They are also highly soluble and will be rapidly diluted and dispersed in the aquatic compartment so that they, in turn, present no environmental risk.

2. Estimating the Concentration of a Substance at the Point of Entry into the Aquatic Environment

The expected introduction concentration (EIC) of an active moiety into the aquatic environment was calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = [illegible] produced for direct use (as active moiety) = the highest quantity of the active moiety expected to be produced for direct use in any of the next five years.

B = 1/liters per day entering POTWs*

C = year/365 days

D = 10^9 µg/kg (conversion factor)

* 1.214×10^{11} liters per day entering publicly owned treatment works (POTWs)

This calculation assumes:

1. All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system.

2. Drug product usage occurs throughout the United States in proportion to the population and amount of wastewater generated.

3. There is no metabolism.

The estimate of the kilogram/year active moiety was based on the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. *Produced for direct use* means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup).

[redacted] to Arnold, Sandra (February 18, 2000)

COMMENT: "Chemistry

Drug Product

2. Based on the stability data provided for the drug product tablets, a 12 month expiry date can be granted."

RESPONSE:

As was suggested by the Division in our meeting of January 18, 2000, we have reviewed the primary and available supportive data that bear on the initial expiration dating period that is to be assigned to mifepristone tablets. As discussed in greater detail below, we believe that we have submitted adequate data to support the [redacted] expiration period requested in the original application, which, as we previously noted in our October 26, 1999 letter (Amendment 35), is the expiration period the European Agency for Evaluation of Medical Products recently assigned to ostensibly the same mifepristone tablet product that is being distributed by Roussel Uclaf's successor in Europe using drug substance and drug product manufactured at new sites. However owing to FDA's interest in the performance of the site-specific tablet batches manufactured at Danco's intended commercial facility, [redacted] be assigned to mifepristone tablets.

We refer to Attachment A of our letter (Amendment 35) dated October 26, 1999, in which we provided summary tables of primary stability data on three mifepristone tablet batches that were submitted in the original application (See Attachment 1). The data from the three Roussel Uclaf batches (RG 21236-12, RG 21236-44, and RG 21236-50), all of which were manufactured using the intended full-scale commercial production process, showed that mifepristone tablets were stable through sixty (60) months storage at 23°C. The original submission concluded that these data supported a 36 month expiration period for mifepristone tablets. In its approvable letter issued to the Population Council on September 18, 1996, FDA did not object or otherwise suggest that the data presented in the original application did not support an expiration period of 36 months.

[redacted] to Arnold, Sandra (February 18, 2000)

In the time since the original application, the full-scale commercial process has been transferred to Danco's contract tablet manufacturer. Owing to the need to retain consistency between the primary stability and commercial batches, Danco sought and obtained equipment of the same operating principle and class, and, in some instances, manufactured by the same equipment fabricator, in order to replicate the full-scale commercial production process. As was established by the data submitted in our letter (Amendment 40) of January 28, 2000, Danco's mifepristone tablets production batches 99005 and 99007, both of which were manufactured using the transferred manufacturing process, continue to exhibit acceptable analytical and physical performance, which is comparable to the primary stability data on the tablet batches submitted in the original application (See Attachment 2).

We believe that the particular issues raised in our application are addressed in FDA's June 1998 Draft Guidance, "Stability Testing of Drug Substances and Drug Products (Draft Stability Guidance). Under the Draft Stability Guidance, if, as here, the primary stability batches are not made at the intended commercial site, then stability data from batches manufactured at that intended commercial site (e.g., site-specific batches) may be used to demonstrate that the drug product made at each site is equivalent. In such cases, if 12 months of long-term data and 6 months accelerated data on three primary stability batches made at other than the intended commercial site are submitted in the original application, a reduced number of site-specific batches with shorter duration of data than that of the primary batches may be acceptable to establish equivalence, provided that the product is a "simple dosage form" (i.e., immediate release tablet). Under the Draft Stability Guidance, a "reduced number of site-specific batches" may be as little as 3 months of accelerated (from a 6-month study) and long-term data on a single site-specific batch.

We recognize that in certain cases, particularly when both the original NDA batches and a single site-specific batch were manufactured at pilot scale, FDA properly might request additional data from the production-scale process. However, where, as here, all primary stability batches were manufactured at production-scale, as were the site-specific batches manufactured by Danco's contract manufacturer, we believe that equivalence has been established. Moreover, the stability data submitted on Danco's site-specific batches exceeds both the number of batches and length of time recommended in the Draft Stability Guidance (e.g., batch 99005, 6 months accelerated and long-term data; batch 99007, 3 months accelerated and long-term data reported, and 6 months accelerated and long-term data due in April 2000).

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

to Arnold, Sandra (February 18, 2000)

COMMENT: "Chemistry

Drug Product

3. The proposal for extending the expiry date based on stability data from one batch (#99005), [redacted], is not acceptable. To address this issue, add the following statement to your proposed stability commitment:

   Extend the expiration dating based upon full shelf-life data obtained from three post-approval production batches covering the entire extended shelf life and tested according to the approved stability protocol.

   Submit the complete revised stability commitment."

RESPONSE:

We have attached a modified and updated stability commitment that includes a new subsection G of the stability commitment, which reads as follows:

> Extension of the expiration dating period will be based upon full shelf-life data obtained from three production batches covering the entire extended shelf-life and tested according to the approved stability protocol.

We are planning to continue the relevant stability studies on batches 99005 and 99007 until such time as sufficient long-term data can be submitted to the agency to justify extension of the expiration period as provided in 21 C.F.R. § 314.70.[1] In proposing this

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[1] Under FDAMA, 21 C.F.R. § 314.70 required revision by November 21, 1999, but a final rule has not yet been promulgated by FDA. For the purposes of this discussion, any reference to the "current" or existing regulation is to 21 C.F.R. § 314.70 as it appears in the 1999 Code of Federal Regulations. We also assume that extensions of expiration periods will remain subject to this regulation, once promulgated by FDA.

language under new subsection G of the stability commitment, we respectfully disagree with the Division's view that any such extension may only be based upon post-approval production batches.

The text of 21 C.F.R. § 314.70(d)(5) only requires that an extension be based upon full shelf life data obtained from the protocol in the approved application. The most natural reading of the regulation indicates that FDA has not imposed any requirement that an extension of an expiration dating period be based solely upon post-approval batches. Moreover, FDA's pending proposed rule modifying 21 C.F.R. § 314.70(d), while adding the requirement that the batches upon which extensions will be based should be "production batches," does not impose any requirement that such batches must be manufactured post-approval. Thus, the only requirement pertaining to the extension of an expiration period is for data from "full production batches," a term not defined in the present or proposed regulation.

For the purpose of extending an expiration period, the Draft Stability Guidance defines a "production batch" as "a batch of...drug product manufactured at the scale typically encountered in a facility intended for marketing production." Plainly, this definition does not require that such batches be manufactured post-approval. Rather, the distinction focuses solely on whether the manufacturing methods and facilities are those "intended" for market production, not whether batches were filed prior to NDA approval.

More importantly, FDA has recognized that a firm may, in certain circumstances, rely upon the continuing results from NDA stability studies in order to justify post-approval extensions of expiration periods. The Draft Stability Guidance expressly states that it is appropriate to rely on the data from stability studies on pilot scale batches continued after NDA/BLA approval as the basis for extending the tentative expiration dating period, provided that any such extension be confirmed with full long-term data from production batches.

We recognize that, as stated in the Draft Stability Guidance, an applicant's reliance on data from pilot-scale batches to extend an expiration period is contingent upon confirmation by data from production batches. We believe that FDA's need for confirmatory data stems from an underlying concern that the transition from pilot to full-scale production may introduce batch variation that only can be detected through accelerated and long-term data from the first production batches. In such cases, we would agree that it may be appropriate for FDA to confirm, through data obtained from

to Arnold, Sandra (February 18, 2000)

---

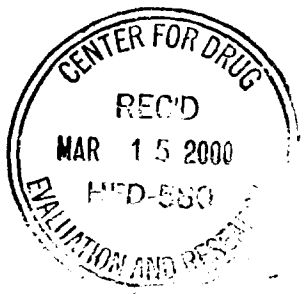
production batches, that any "tentative" expiration period derived from the continued study of NDA pilot-scale batches is appropriate.

However, here the subject production batches submitted in the application were manufactured at the intended commercial manufacturing facility, using equipment and production methods that are fully representative of any batches that will be manufactured after NDA approval. In the absence of a substantive difference between pre- and post-approval production batches, any concerns regarding batch to batch variation is illusory. Thus, there would appear to be no scientific or technical justification for refusing to consider pre-approval production batches for the purposes of extending the initial expiration period. Moreover, FDA regulations and guidance do not support the Division's view, and, in our view, any limitation of our ability to extend the expiration period based solely upon data obtained from post-approval production batches is unwarranted.

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

faxed 3/20/00



March 10, 2000

ORIGINAL

Division of Reproductive and Urologic
Drug Products
HFD 580
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

NC

Att: Document Control Room 17B-20

Re: NDA 20-687

This is to let you know that Nancy L. Buc, of the law firm of Buc & Beardsley, 919 Eighteenth Street NW, Suite 600, Washington, DC 20006 is representing the Population Council and the Danco Group in connection with this NDA and is authorized to communicate with the FDA on any issue pertaining to the NDA.

Very truly yours,

Sandra Arnold

cc: Nancy L. Buc, Esq.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

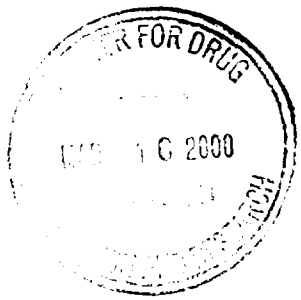
CSO INITIALS DATE

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

Danco Laboratories, LLC

ORIGINAL

March 9, 2000



NEW CORRESP

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

- Request for Teleconference with

Dea

As discussed today, given that is no longer heading the Division of Reproductive and Urologic Drug Products, I would very much like to have the opportunity to have a teleconference with as now specifically responsible for this product.

The objectives of the teleconference are to establish a positive relationship with for the upcoming period of review and action by the FDA and to review the overall status of the project with the goal of moving it forward as rapidly as possible.

I would appreciate it if you could arrange for this teleconference to be held at the earliest opportunity and look forward to receiving suggested dates and times.

Sincerely

President and Chief Executive Officer

/dns

cc: Sandra P. Arnold

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS

DATE

Danco Laboratories, LLC

March 6, 2000

ORIGINAL

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

Dear [redacted]

Please replace the letter you received yesterday with this document, which includes the attachment that was previously inadvertently omitted.

Thank you.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

Cc. [redacted]

Sandra P. Arnold – Population Council

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☒ N.A.L. ☐ ACTION
CSO INITIALS 3/13/00

MIF 007674

Danco Laboratories, LLC

March 3, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

Dear

During a telephone conversation you and I had on approximately February 15, either you or had mentioned that once it had passed inspection, Danco's substance manufacturer would be the first substance facility in China to be in compliance with the FDA's current Good Manufacturing Practices (cGMP). I responded that it was Danco's understanding that there were numerous final substance (not intermediate) plants in China that were in compliance with the FDA's cGMP requirements. I further advised that our consultant, was himself involved in several plants which were successfully inspected by the FDA.

has now provided me with a list of his "final substance" clients in China who have been successfully audited by the FDA. The list is from 1987 to 1999 and includes at leas substances a plants, with plants being successfully audited in 1999 and n 1998. This list only includes plants that Danco knows of through work; we assume that there may also be additional plants in China that have had successful FDA audits. has given me permission to release this list to you.

During the same conversation, you indicated that you believed the inspector visiting the plant was hampered by the lack of English translations of plant documents and that we should translate all the plant documents ahead of the next inspection. I responded that it was Danco's understanding from and others that translations were not necessary for such audits provided that a translator was present. At your suggestion I contacted Foreign Inspection Team, who

confirmed that translations are not required as long as an interpreter is provided. [redacted] further counseled me not to undertake any translations at the plant until he received the re-inspection request letter from DRUDP, following which he would be in a better position to advise Danco what, if anything, needs to be translated ahead of the re-inspection. We understand that you will be issuing this letter today (March 3).

I am providing this information to clarify our previous conversations on these matters.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

Cc: [redacted]

Sandra P. Arnold – Population Council

Danco Laboratories, LLC

March 3, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets

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I am providing this information to clarify our previous conversations on these matters.

Sincerely

/S/

President and Chief Executive Officer

/dns
Enclosure

Cc:

Sandra P. Arnold – Population Council

APPEARS THIS WAY
ON ORIGINAL

facsimile
MESSAGE

Date: February 23, 2000

Company: Danco Investors Group, L.P.

Attention: President & Chief Executive Officer

Fax No.:

Pages (including cover sheet): 4

Re: FDA Inspections: China

Dear

In connection with our today's telephone conversation, please find hereafter faxed the requested list and E-mail of February 18.

Thank you for your attention.

Sincerely,

Executive Assistant

Encl.

FDA INSPECTIONS: CHINA

1987	Fuzhou Antibiotic Factory
1987	Southwest Synthetic Pharm. Gen. Factory
1987	Suzhou Biochemical Pharm. Factory
1988	Sichuan Pharmaceutical Co., Ltd.
1990	Nanjing Pharmaceutical Factory
1990	Shanghai No. 2 Pharm. Factory
1990	Sichuan Pharmaceutical Co., Ltd.
1991	Nanjing Pharmaceutical Factory
1992	Sichuan Pharmaceutical Co., Ltd.
1994	Southwest Synthetic Pharm. Gen. Factory
1995	Nanjing Pharmaceutical Factory
1995	Long March Pharmaceutical Plant

* No Inspectional Observations issued

FDA INSPECTIONS: CHINA (Cont.)	
1996	Sichuan Pharmaceutical Co., Ltd.
1998	Shaanxi Hanjiang Pharmaceutical Ltd.
1998	Long March Pharmaceutical Plant
1998	Southwest Synthetic Pharm. Gen. Factory
1999	Sichuan Pharmaceutical Co., Ltd.
1999	Suzhou No. 4 Pharmaceutical Factory
1999	Shandong Xinhua Pharmaceutical Factory
1999	Tianjin Pharmaceutical Corporation

* No Inspectional Observations issued

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

February 24, 2000

VIA FEDERAL EXPRESS

Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Room 13B-28
Rockville, MD 20857

NEW CORRESP
1/C

Re: NDA 20-687, Mifepristone 200mg Oral Tablet
- **Amendment 042 - Notification Of Intent To File An Amendment**

Dear

Pursuant to 21 C.F.R. § 314.110, the Population Council hereby gives notice of its intention to file an amendment addressing the issues cited in the February 18, 2000, approvable letter. The Population Council will be contacting Project Manager, Division of Reproductive and Urologic Drug Products to seek clarification of some of the deficiencies listed in the approvable letter to assure that our responses will be complete.

We appreciate your consideration of the NDA and seek to work diligently to rapidly resolve the outstanding deficiencies.

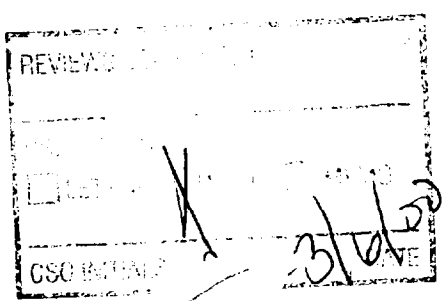
Very truly yours,

Sandra Arnold

Enclosure

cc:

Frederick Schmidt, Population Council



This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Group, LLC requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45.Contact telephone number is

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CONCEP

1/C

February 16, 2000

VIA FAX and FEDERAL EXPRESS

Division of Reproductive and
Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

withdrawn
2/23/00

Subject: NDA 20-687, Mifepristone 200 mg Oral Tablets
Amendment Number: 041
Patent Information/Debarment Certification

Dear

We refer to our above-mentioned New Drug Application for Mifepristone Tablets and to the telephone conversation of February 15, 2000 with of your division regarding the status of patent information and the debarment certification in the application. With this submission, we wish to provide the following information:

1. **Patent Information**

   Patent information for the application was provided in our initial application (Volume 1.1, Page 4), dated March 14, 1996. We certify that there has been no change in the information provided in that submission and that the information remains current with respect to the application.

2. **Debarment Certification**

   The debarment certification statement for our application was provided in Amendment 003, dated August 15, 1996. We certify that the statement provided in that submission remains current with respect to the application.

Please contact me should there be any questions or comments regarding this submission.

Very truly yours,

Sandra Arnold

cc: The Danco Group

REVIEWS

One Dag Hammarskj[illegible] ew York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcoun[illegible] http://www.popcouncil.org

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	February 16, 2000
TELEPHONE NO. *(Include Area Code)* (212) 339-0663	**FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* One Dag Hammarskjold Plaza New York, NY 10017	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Mifepristone	Not available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	200 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Induction of abortion

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 007684

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbioblogy (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Patent Information/Debarment Certification

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sandra Arnold	Sandra P. Arnold, Vice President	2/16/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Dag Hammarskjold Plaza, New York, NY 10017	(212) 339-0663

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

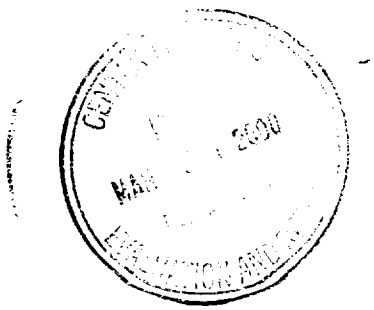
FORM FDA 356h (7/97)

MIF 007685

The Danco Group

March 30, 2000

noted
3/21/00



Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

Re: NDA 20-687, Mifepristone 200mg Oral Tablets A2

- Amendment 043 - Response To Approvable Letter Dated February 18, 2000

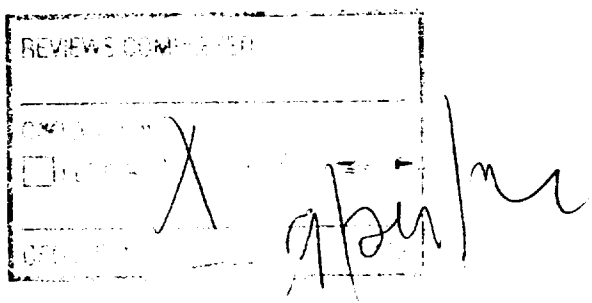
Dear

This Amendment 043 is the complete response to the Approvable Letter dated February 18, 2000. It is comprised of one volume of responses plus two volumes of Safety Update Report #3 and one volume of International Product Labeling.

Please don't hesitate to contact me if you have any questions on the submitted material.

Sincerely,

President and Chief Executive Officer



/dns
Enclosures

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

Nancy L. Buc, Esq. – Buc & Beardsley

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

MIFEPRISTONE

PERIODIC SAFETY UPDATE REPORT N° 9

1st of September 1998 to the 30th of November 1999

PSUR n° 9 \ MIFEPRISTONE \ 28/12/99

December 1999

28 DECEMBER 1999

001

TABLE OF CONTENTS

003

MIF 007689

1 - INTRODUCTION

This report is the ninth Periodic Safety Update Report (PSUR 9) on Mifepristone compiled for regulatory authorities since January 1991. It summarises the safety data received by the Medical Department at Exelgyn from worldwide sources, which occurred between September 1 1998. till November 30 1999

Mifepristone (RU 486) is a potent antiprogestin, available as 200 mg tablets for oral administration. Mifepristone is being marketed by Exelgyn and was developed by HMR. The Population Council (USA) has also rights to mifepristone under a special agreement.

The initial and main indication for mifepristone is medical alternative to surgical termination of early intra-uterine pregnancy (first approval in France in December 1988), in combination with a prostaglandin analogue (misoprostol or gemeprost). This combination leads to successful pregnancy termination in more than 95% of cases.

Mifepristone has also been approved for therapeutic termination of pregnancy beyond the first trimester in combination with prostaglandin analogues in order to reduce their doses, softening and dilatation of the cervix uteri prior to surgical pregnancy termination and induction of labour for foetal death in utero.

This report is compiled in a format alike that proposed by ICH3 Topic E2C (Step 4 Document issued in November 1996).

2 - WORLD-WIDE MARKET AUTHORISATION STATUS

The cumulative world-wide market authorisation status of mifepristone specifying the respective dates of approval and dates of launch is presented in Appendix 10.1.
Since the last report the following changes occurred:
A European market authorisation (MA) has been obtained on July 6, 1999 for a selected number of countries through the mutual recognition procedure (MRP), where France acted as a Reference Member State (RMS).
These countries are Austria, Belgium, Denmark, Finland, Germany, Greece, Netherlands and Spain.
The national marketing authorisation dates are indicated in appendix (10.1.1 and 10.1.2). Other MA were obtained in Israel, Switzerland, Russia. The product has been introduced only in a few of the above listed countries, the respective dates of launch are indicated in Appendix 10.1.2.
The product labelling is slightly different in Israel, and Russia; the Swiss text is closer to the one approved as the European SPC (see Appendix 10.1.3).
In addition, renewal of the MA in the UK was obtained in May 1999.
The indication "Labour induction for fetal death in utero" has been restricted during the MRP with the added sentence "when prostaglandins or oxytocyn cannot be used" This changed is not related to any safety issue but reflects the common practice in most of the EU member states

3 - UPDATE OF REGULATORY OR MANUFACTURER ACTIONS TAKEN FOR SAFETY REASONS

During the period of review, there has been no specific actions taken for safety reasons. There was no marketing authorisation rejection, withdrawal or suspension, nor restrictions to distribution, nor clinical trial suspension, nor dosage or formulation modification, nor changes in target population or indications. However the indication "Softening and dilatation of the cervix uteri prior to voluntary pregnancy termination by vacuum aspiration" has been approved in France at the single dose of 200 mg. in November 1998.

4 - REFERENCE SAFETY INFORMATION

The Master Data Sheet is presented in Appendix 10.2.1. The Master data sheet which was revised in 1998 to be in line with the document proposed in the mutual recognition procedure, has been modified again in the sections "pharmacological properties" and "lactation" according to the reassessment of the dossier. These sections reflect now the approved European SPC (Appendix 10.2.2), the new text does not introduce new important safety information but rather aims to be more accurate and explanatory

5 - PATIENT EXPOSURE

A crude estimate of the number of patients treated with Mifepristone has been calculated from the sales volumes, in units, of drug sold in the period 01 September 1998 to 30th November 1999. More recent sales data are unavailable. It has been assumed that each patient has received the standard dose of 600 mg. This may underestimates the number of patients exposed to the drug. Indeed, in the UK many physicians use a lower dose of 200mg. Also since the approval of the indication "Softening and dilatation of the cervix" at the dose of 200 mg in France, a number of patients received only one tablet.

5.1. CLINICAL TRIALS

From information obtained by the manufacturer, it is estimated that 1318 patients received mifepristone during the review period: 01 September 1998 to the 30th of November 1999. None of these trials is conducted by the manufacturer, but are performed under the responsibility of individual investigators or organisations. Only the medication is provided by Exelgyn.
Information regarding these studies is presented in Appendix 10.3.1 and 10.3.2.

5.2. MARKET EXPERIENCE

In 15 months covered by this review period, from the 01 September 1998 to the 30th of November 1999, mifepristone sales amount to ——
Assuming one unit represents one treatment course, this would correspond to —— women administered mifepristone.

9.8. EXPERIENCE IN SPECIAL PATIENT GROUPS

Two patients with a minor form of Willebrand disease and one patient with Protein C deficiency were administered mifepristone, treatment showed to be uneventful in these patients.

9.9. CONCLUSION

No area of safety concern has been identified during the period of review. The data presented in this report are consistent with the cumulative experience to date and provide no information, which could alter the risk-benefit ratio of mifepristone.

10. APPENDICES

APPENDIX 10.1

CUMULATIVE REGULATORY APPROVAL / DECISION DATES

APPENDIX 10.1.1.

REGISTRATION STATUS UP TO 1998

MIFEGYNE®
REGISTRATION STATUS AS OF NOVEMBER 1998

COUNTRY	DOSAGE PER TABLET	DATE OF			INDICATIONS (and POSOLOGY)
		APPROVAL	LAUNCH	TRANSFER OF MARKETING AUTHORIZATION	
FRANCE	200mg	December 28, 1988	September 1989	8/8/97	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 49 days amenorrhea (600mg single dose)
		July 17, 1992		CIP N°556 473.0	• Preparation for the prostaglandin action in therapeutic pregnancy termination (600mg single dose)
					• Fœtal death in utero (600mg x 2 days)
		November 6, 1998			• Softening and dilatation of the cervix uteri prior to voluntary pregnancy termination by vacuum aspiration during the first trimester (200mg single dose)
U.K.	200mg	July 1st, 1991	July 1991	24/09/97	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose)
		August 4, 1995		PL 16152/0001	• Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination (600mg single dose)
					• Termination of pregnancy between 13 and 20 weeks gestation in combination with gemeprost (600mg single dose)
SWEDEN	200mg	September 4, 1992	October 1992	1/10/97 ASP 91-0246	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600mg single dose)
					• Termination of pregnancy in the second trimester (600mg single dose)
	600mg	August 2, 1995		ASP95-0005	Same indications as for 200mg tablets
U.S.A.	200mg	Approvable letter September 18, 1996			• Medical termination of intra-uterine pregnancy through 49 days duration of pregnancy

APPENDIX 10.1.2.

NEW REGISTRATION AND LAUNCH DATES

MIFEGYNE®
REGISTRATION STATUS AS OF DECEMBER 1999

COUNTRY	DATE OF SUBMISSION	DATE OF APPROVAL	PLANNED / ACTUAL DATE OF LAUNCH	LICENSE NUMBER
E U R O P E				
MRP	**April 6, 1999**	**July 6, 1999**		**FR/H/137/01**
AUSTRIA	" "	21/09/99	December 99	1-23220
BELGIUM	" "	22/11/99	Q_2 2000	2 532 IE 1 F3
DENMARK	" "	27/08/99	February 2000	30 741
FINLAND	" "	20/12/99	February 2000	MTnr 14064 FIN
FRANCE	-	*28/12/88* *Update 25/10/99*	*Marketed 1989*	*556 473.0*
GERMANY	" "	19/08/99	November 99	46 038 .00.00
NETHERLANDS	" "	25/08/99	December 99	RVG 24 206
SPAIN	" "	21/10/99	Q_1 2000	62.278
SWEDEN	—	*1992*	*Marketed 1992*	*125 370*
UK	—	*1991* *Update 1999/08*	*Marketed 1991*	*PL 16152 / 0001*
O T H E R S				
ISRAEL	07/02/99	10/08/99	September 99	115 52 29641 00
RUSSIA	22/11/98	14/04/99	September 99	P-8-242 N°01 1033
SWITZERLAND	10/02/99	14/07/99	October 99	55205
TUNISIA	06/08/99	Approvable November 99		
UKRAINIA	05/99			

APPENDIX 10.1.3.

DIFFERENCES IN THE LABELING OF THE EUROPEAN SPC AND OTHER COUNTRIES