ATTACHMENT D: Articles Regarding Onset of Puberty

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ROUSSEL UCLAF

Direction du Développement Préclinique

RU 38486

STUDY OF THE DEVELOPMENT AND FERTILITY OF YOUNG RATS TREATED SUBCUTANEOUSLY WITH A SINGLE INJECTION ON DAY 1 AFTER BIRTH

(1, 10, 100 mg/kg)

B. VANNIER - F. SPEZIA - R. BREMAUD
H. THIEN-AUBERT - G. BODE

Reference: 92/4183/TX

Date: October 1994

Number of pages: 120

SUMMARY

The aim of this study was to evaluate the potential effects of RU 38486 (mifepristone, a synthetic steroid with an antiprogestational action) on the development and the integrity of reproductive function of young male and female rats treated subcutaneously with RU 38486.

RU 38486 was administered at doses of 1, 10 and 100 mg/kg on Day 1 after their birth. The effects of this treatment on physical development, puberty and reproductive function were observed.

Under the experimental conditions of this study, RU 38486 did not affect the general development of the young animals. A tendency to early onset of puberty was apparent in the females treated with 100 mg/kg. No effect was noted in the males. Reproductive function was perfectly normal in both sexes

SYNOPSIS

Study no:	92/4183/TX
Compound:	RU 38486
Batch no. (Control number):	8 V 1238 B
Activity:	Antiprogesterone
Species, race:	Rat, Sprague-Dawley OFA, S.P.F. Caw
Number of animals:	The offspring of 14 to 15 litters, i.e. about 200 young per group.
Treatment	
Doses:	0, 1, 10 and 100 mg/kg/day.
Route:	Subcutaneous
Period:	Day 1 after birth
Number of administrations:	One only, in a volume of 6 ml/kg
Formulation:	In solution in maize oil

RESULTS

The general condition and growth of the F1 offspring were similar in the controls and treated animals.

The onset of puberty, evaluated in the males by the date of testicular descent into the scrotum, was not affected by treatment. In the females, vaginal opening occurred slightly earlier in the animals treated with 100 mg/kg.

At the age of 11 or 15 weeks, histopathological examination of the testes revealed a normal structure; the activity of the seminiferous tubules was the same in the controls and treated animals. Reproductive function, assessed by mating rate and fertilising capacity, was not affected by treatment.

CONCLUSION

Under the experimental conditions of this study, RU 38486 did not impair the general development of the young animals. A tendency to early onset of puberty was apparent in the females treated with 100 mg/kg. No effect was noted in the males. Reproductive function was perfectly normal in both sexes.

STUDY LOCATION AND FILING: ROUSSEL UCLAF
Toxicology Department
102/111 Route de Noisy
93235 ROMAINVILLE cedex (France)

AUTHORS

B. VANNIER	Head of Reproduction Toxicology, Cellular and Genetic Toxicology;
F. SPEZIA	Head of Reproduction Toxicology Laboratory;
R. BREMAUD	Senior Member of Reproduction Toxicology Laboratory;
H. THIEN-AUBERT	Head of Pathology Laboratory,
D. TREMBLAY	Head of Preclinical Development.

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: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 27, 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 Hammarskjol Plaza New York, New York 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)* Mifepristone	PROPRIETARY NAME *(trade name)* IF ANY Not Available

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
11β-[p-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

CODE NAME *(If any)* -

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

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 (Full establishment information should be provided in the body of the Application.)
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 001421

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 Microbiology (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 report 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)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Documentation for FDA Meeting on August 4, 2000.

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 Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 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 FD&C Act Section 506A, 21 CFR 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 review 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	07/27/2000

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

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Biopharm labeling

NDA 20-687

INFORMATION REQUEST LETTER

JUL 25 2000

Population Council
Attention: Sandra P. Arnold,
VP Corporate Affairs
One Dag Hammarskjold Plaza
New York, New York 10017

Dear Ms. Arnold:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone Tablets.

We also refer to our July 19, 2000, meeting with representatives from the Population Council, Danco Laboratories, LLC, and Ms. Nancy Buc. From the meeting, one of our action items was to determine whether information regarding the metabolic pathway for Mifepristone and potential drug interactions should be added to the drug labeling. We completed review of recent literature and conclude that the following revisions to the professional labeling are needed (deletions are shown with strike-out, additions are underlined):

1. CLINICAL PHARMACOLOGY; Metabolism subsection:

2. PRECAUTIONS; Drug Interactions subsection:

Appropriate revisions are also needed for the patient information sheet (patient package insert) to incorporate the information about potential drug/food interactions related to metabolism of mifepristone.

In addition, in a telephone conversation with Ms. Shelly Clark of the Population Council I conveyed the following revision requested for the patient agreement. The revisions are to the sixth bullet of the draft agreement (exhibit H) of the briefing materials submitted July 5, 2000, for the July 19, 2000, meeting as follows (deletions are shown with strike-out, additions are underlined):

Please include the above requests, with any comments you have, in the pre-meeting materials you will be submitting on July 28, 2000, in preparation for our next meeting on August 4, 2000.

If you have any questions, call me, at

Sincerely,

/S/ 7/25/00

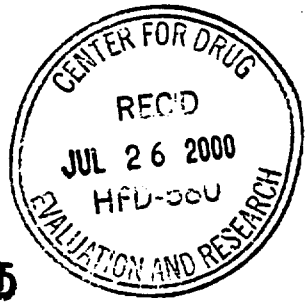
Regulatory Affairs
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

July 25, 2000

ORIGINAL



Office of Drug Evaluation III
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20 ORIG AMENDMENT
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 053 - Additional Stability Data on Drug Product
- Revised Stability Commitment
- Mock-Up Sample of the Primary Package and its Blister Card

Dear ———

Pursuant to our telephone conversation with ——— on July 20, 2000, we are providing the agency with the following information:

A. Additional Stability Data on Drug Product

Twelve (12) and nine (9) month long term stability data on Danco's Drug Product Lots #99005 and #99007, respectively, are enclosed (see Attachment A). Six (6) month accelerated data on these same two production-scale lots were previously supplied in Amendment 040 dated January 28, 2000 (Lot #99005) and Amendment 044 dated April 20, 2000 (Lot #99007).

These new data continue to show excellent long-term stability performance for Danco Drug Product. These results, as well as the previously provided stability data on Roussel Drug Product, demonstrate that the initial expiration dating period should be established at eighteen (18) months.

B. Revised Stability Commitment

We have revised the Stability Commitment (see Attachment B) to clearly indicate that a Prior Approval Supplement will be filed with FDA if Danco wishes to use pre-approval batch data to request extension of the initial expiration dating period.

In addition, we have corrected the typographical error in the cover page to Attachment C of Amendment 047, dated May 17,2000, to read "Drug Product" rather than "Drug Substance" (see Attachment C)

C. Mock-Up Sample of the Primary Package and its Blister Card (See Enclosure)

Each blister card has a designated "print area" where the following information will be printed: (1) the Lot/ID number (11 digits), (2) the expiration date and (3) the "data matrix square" represented by "▣". The unique Lot/ID number is composed of the Lot number (first five (5) digits) and an additional six (6) digits for each individual card. All of this information also is reflected in the code printed in the data matrix square. The code in the data matrix square is readable by a hand held scanner and permits the tracking of each individual blister card. This designated "print area" of the blister card is visible through a cutout window of the primary package, thus providing easy access and readability for batch information. This is more fully described in the previously submitted Distribution Plan.

Since the original production of the mock-up of the blister card and primary package, we have made the following changes which will appear on the final packaging:

- "MIFEPREX® (Mifepristone Tablets 200mg)" that appears on the package and the blister has been changed to "MIFEPREX® (Mifepristone) Tablets, 200mg".
- The following storage statement has been added to the blister card: " Store at 25°C (77°F)" .

We believe that the trademark is prominently placed on the primary package and that a location change would not improve its prominence.

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

Sincerely

/s/

President and Chief Executive Officer

/dns
Enclosure
cc: Sandra P. Arnold — Population Council

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Danco Laboratories, LLC

[ ]

TELEPHONE [redacted] FACSIMILE [redacted]

FACSIMILE TRANSMISSION

FROM: [redacted] DATE: July 18, 2000

TOTAL PAGES (Including This Cover Sheet): 4

NAME	COMPANY	FAX #	TIME SENT
[redacted]	FDA	[redacted]	

MESSAGE:

Dear [redacted]

I thought it would be useful for you to have the information you and [redacted] requested, ahead of tomorrow's meeting.

Sincerely,

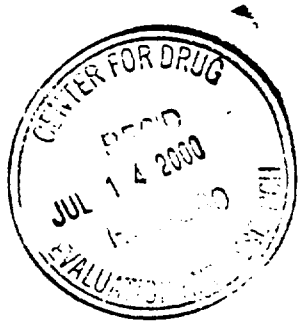
/s/

President and Chief Executive Officer

cc: Sandra F. Arnold - Population Council

Danco Laboratories, LLC

July 13, 2000



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
BC

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

- Amendment 052 - Submission of Additional Testing and Stability Data on Post Process Adjustment Drug Substance

Dear ———

Consistent with the commitments made in Amendment 050 dated July 5, 2000 this Amendment 052 provides additional information on mifepristone Drug Substance manufactured by the adjusted process which was described in Amendment 048, dated June 22, 2000. As we have previously discussed with ———, this additional information is intended to establish a link between the pre process adjustment and post process adjustment Drug Substance.

A- Post Process Adjustment Drug Substance Physical and Analytical Data

As per our commitments in Amendment 050, we are providing certain physical and analytical data on three batches of post process adjustment Drug Substance. The batches tested are #000501, #000502 and #000503.

[

]

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, LLC requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is ———

B. Post Process Adjustment Drug Substance Stability Data

As per our commitment in Amendment 050, we are now providing the three-month accelerated and long-term stability data on one post process adjustment batch, #000105 (See Attachment 5). These data show that there are no significant changes or trends from the zero time data after three months under either accelerated or long-term storage conditions. This is consistent with the results observed in both the accelerated and long-term studies on pre process adjustment batches, which are also included in Attachment 5.

Six month accelerated and long-term stability data for this batch #000105 is due by the end of July and will be reported to the FDA as soon as it is available during August. Furthermore, as we stated in Amendment 050, two month long term and accelerated stability data on three additional batches will be provided by the end of August followed by three-month data by the end of September. Additionally, a three batch accelerated stability study recently begun in the U.S. will provide three months data in mid-October.

In summary, we believe that all of the post process adjustment Drug Substance physical and analytical data presented in A above together with the post process adjustment Drug Substance stability data presented in B above demonstrate:

- the comparability and consistency of Drug Substance batches manufactured before and after the process adjustments and
- that Drug Substance from either the pre or post adjustment process is acceptable for use in manufacturing finished Danco Drug Product.

As per our commitment in Amendment 050, we plan to manufacture a production batch of Drug Product using post process adjustment Drug Substance within the next month. Tablets from this Drug Product batch will be subjected to a S-2 level dissolution study and we plan to report this data to the FDA by the end of August.

Separately, and in response to ——— question concerning Drug Substance batch dating by the manufacturer, we advise that the ———

———

——— For example Drug Substance Batch # 000503 was the ———

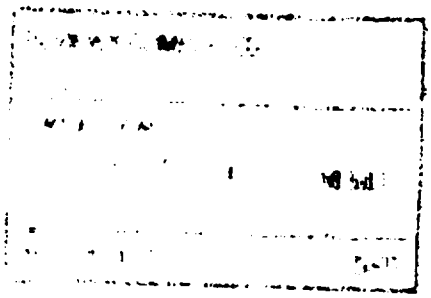
Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

President and Chief Executive Officer

cc: Sandra P. Arnold – Population Council



Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

July 11, 2000

BY HAND

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

NEW CORRESP
NC

Re: NDA 20-687, Mifepristone 200 mg oral tablets
Amendment 051, Replacement for Exhibit E to the Distribution Plan
Letter Submitted on July 5, 2000

Dear ———

With apologies for our failure to copy both sides of Exhibit E to the Revised Distribution Plan in our July 5 submission, I am enclosing clean and marked copies of Exhibit E. I would appreciate it if recipients of the July 5 package would substitute them for the previously submitted Exhibit E. Thank you.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

cc:
President and Chief Executive Officer
Danco Laboratories, LLC

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

/S/ 7/13/00
CSO INITIALS DATE

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

Danco Laboratories, LLC

TELEPHONE [redacted] FACSIMILE [redacted]

FACSIMILE TRANSMISSION

FROM: [redacted] DATE: July 7, 2000

TOTAL PAGES (Including This Cover Sheet): 5

NAME	COMPANY	FAX#	TIME SENT
[redacted]	FDA	[redacted]	1 p.m.

MESSAGE:

Dear [redacted]

Attached is Exhibit E from the Distribution Plan, both the clean and the marked-up versions. For facsimile purposes, Exhibit E is 2 separate pages, while in actuality it is one double-sided page, comprised of the Prescriber's Letter and the Order Form. In addition to this fax, we will hand deliver the official submission on Monday.

Sincerely,

/s/

[redacted]

President and Chief Executive Officer

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

July 5, 2000

BY HAND

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

Re: NDA 20-687, Mifepristone 200 mg oral tablets
Amendment 050, Briefing Package for July 19, 2000 Meeting

Dear ———

We are looking forward to meeting with you and your colleagues on July 19 about mifepristone. As you know, we are especially interested in discussing the Distribution Plan and the labeling (including the package insert, the PATIENT INFORMATION sheet, and the PATIENT AGREEMENT). To facilitate that discussion, we are submitting the briefing package for the meeting, as requested in ——— s June 23 letter, including:

1. our letter responding to ——— June 19 letter on labeling, including revised labeling (both clean and marked copies),

2. our June 23 letter on the Distribution Plan

3. a new letter on the Distribution Plan which submits our revised Distribution Plan (both clean and marked copies)

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 addition, I have attached the requested update (prepared by Danco Laboratories, LLC) on CMC and inspection issues. Also enclosed is the requested update on our Phase IV protocols. We do not plan to discuss either of these topics at our meeting, however.

Attending the meeting for the Population Council and Danco will be:

Sandra P. Arnold, Vice President, Corporate Affairs, Population Council
_____, President and Chief Executive Officer, Danco Laboratories, LLC
Beverly Winikoff, M.D., M.P.H., Program Director, Reproductive Health, International Programs Division, Population Council
Richard U. Hausknecht, MD, Medical Director, Danco Laboratories, LLC
Shelley D. Clark, Ph.D., Program Associate, Population Council
Heather M. O'Neill, Director of Public Affairs, Danco Laboratories, LLC
Nancy L. Buc, Buc & Beardsley, Counsel to Population Council and Danco Laboratories, LLC

Sincerely,

Sandra P. Arnold /ss

Sandra P. Arnold

cc:
President and Chief Executive Officer
Danco Laboratories, LLC

APPEARS THIS WAY
ON ORIGINAL

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, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 5, 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, New York 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)* 11β-(p-(dimethylamino)phenyl)-17β-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 NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

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

IF AN ANDA, OR 505(b)(2), 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 ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

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 (Full establishment information should be provided in the body of the Application.)
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)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
X	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 Microbiology (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 report 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)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* Briefing Package For July 19, 2000 Meeting

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 Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 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 Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 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 P. Arnold /.b	Sandra P. Arnold, Vice President	7/5/00
ADDRESS *(Street, City, State, and ZIP Code)*		**Telephone Number**
One Dag Hammarskjold Plaza, New York, NY 10017		(212) 339-0663

NDA 20-687

INFORMATION REQUEST LETTER

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

JUN 30 2000

Dear Ms. Arnold:

Please refer to your March 18, 1996 new drug application for mifepristone tablets.

We also refer to your March 30, 2000 resubmission that addressed the issues outlined in our February 18, 2000 approvable letter.

We are reviewing your proposed labeling for this application and have the following comments and information requests regarding the Carcinogenesis, Mutagenesis, Impairment of Fertility sections of your label. (Recommendations are indicated by ~~strikethrough~~ for deletions and underline for additions. Comments are indicated by [***bracketed, bolded and italicized***] statements.) We need your prompt written response to continue our evaluation of your NDA.

Physician Package Insert

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nursing Mothers

[redacted]

If you have any questions, call [redacted] Project Management Staff, at [redacted].

Sincerely,

/S/ 6/30/00

[redacted]
Project Management Staff
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

INFORMATION REQUEST (IR)

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

June 23, 2000

VIA FEDERAL EXPRESS

Office of Drug Evaluation III
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NEW CORRES?
NC

Re: NDA 20-687 – Mifepristone 200 mg Oral Tablets
Amendment 049 – Response regarding Distribution Requirements

Dear

We have appreciated the opportunity to discuss with you and your colleagues how mifepristone will be labeled and distributed, and we thank you for sending to us by fax the Agency's unofficial list of distribution proposals and the minutes of our June 1 telephone call. As you suggested, we are providing in this letter our views on why certain of the proposals you sent us seem unnecessary from a safety standpoint and will likely also significantly impair women's access to this very important - and very safe and effective - drug. As we're sure you know, has set up a meeting for July 19, so that we can continue our discussions.

In considering what information should be provided to physicians and other health care providers and to women who are considering medical abortion with mifepristone, and whether and what kinds of distribution requirements should be imposed, we think it is useful to begin with a recapitulation of the areas where agreement between us is already apparent.

First, we are in agreement that mifepristone with misoprostol is clearly safe and effective in inducing complete medical abortion. The draft package insert proposed by FDA in its February 18, 2000 approvable letter and the draft package insert we proposed in our March 30, 2000 response agree that more than 92% of subjects had complete medical abortions. Second, we are in agreement that the most common "adverse reactions" to mifepristone, vaginal bleeding and uterine cramping, are necessary to

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

produce the abortion and are expected consequences of the treatment. Although for many women (about 80-90%) the bleeding is heavier than they experience during normal menstrual periods, it is only about 5.5% whose hemoglobin decreases by more than 2 g/dL, and only very rarely that bleeding is heavy enough to require administration of vasoconstrictor drugs, curettage, saline infusions, and/or blood transfusions. We also agree that women whose pregnancy is not ended by the mifepristone/misoprostol regimen should be strongly advised to have their pregnancy terminated by surgical abortion.

We also apparently agree that our proposed Distribution Plan, which was submitted in January 2000 and discussed in our March 30 response to the February, 2000 approvable letter, adequately addresses issues of "physical" security and tracking to the point of receipt by the physician. In addition, we agree that physicians who prescribe mifepristone should have ready access to adequate information and training to prescribe the drug, and we agree that women considering medical abortion should receive complete and accurate information.

We also believe that because mifepristone is such a safe and effective drug, it is important that women seeking to exercise their personal and constitutional right to choose an abortion have ready access to this new (in the United States) option. Any limitation or restriction that makes mifepristone harder to obtain than other approved drugs will reduce that access to some degree, and although we agree with you that some limitations and restrictions may be appropriate, we believe it is important not to add any limitations or restrictions which are not essential. It is for this reason that we want to take you up on your suggestion to discuss FDA's proposals, for we believe that some of them are overly regulatory and disproportionate to and unnecessary in light of the straightforward safety and efficacy profile of mifepristone.

Perhaps the clearest example of a requirement that is overly regulatory is the suggestion that physicians provide a copy of their license as a prerequisite to receiving mifepristone. As you know, the Distribution Plan we submitted requires the physician to read and sign a letter (Exhibit E to the Distribution Plan[1]) concerning provider qualifications and treatment guidelines on which he or she is required to provide his or her license number. That requirement alone would impose a burden on

[1]A copy of the pertinent section of the Distribution Plan (Section IV and Exhibits) is attached for your convenience. Exhibit E is titled "Account Registration Letter"; in this letter we refer to it as the Prescriber's Letter.

mifepristone that is unusual in FDA regulation; for most if not all drugs, FDA assumes that prescribers are licensed to prescribe and dispensers are licensed to dispense. Indeed, had we not proposed it, FDA's insisting on provision of the license number would have been inappropriate, and there seems to be no reason for FDA to distrust - to the point of requiring confirmation - the license information provided by prescribers. By way of comparison, the Drug Enforcement Administration does not require prescribers to submit a copy of their state license in the context of obtaining a DEA number to prescribe narcotics and other drugs susceptible of diversion and abuse,[2] and we do not think FDA should require a copy of a license as a condition of obtaining a safe drug which has no abuse potential and is unlikely to be diverted.

Whether to prescribe mifepristone is a decision physicians are obviously wrestling with, and we think it fair to say that many prescribers are hardly rushing to do so. Imposing unnecessary regulatory burdens on mifepristone prescribing, such as providing a copy of a state license to practice medicine or some of the other FDA proposals, will only diminish their already muted enthusiasm and have the result of further reducing access.

A second central issue is that of physician training in prescribing mifepristone. As the Distribution Plan explains, training in medical abortion, including use of mifepristone, has been well underway for some time in anticipation of FDA's approval of this NDA. Using unrestricted grants from Danco and their own resources, the National Abortion Federation (NAF) and the Consortium of Planned Parenthood Abortion Providers (CAPS) have held numerous training programs across the country in medical abortion using mifepristone. Other organizations which have already provided or soon will provide training on mifepristone include the American College of Obstetricians and Gynecologists, the American Medical Women's Association, and the Association of Reproductive Health Professionals. In addition, the peer-reviewed American Journal of Obstetrics and Gynecology will publish in August 2000 a supplement on medical abortion with mifepristone; it will contain 11 articles by leading experts. Also, NAF and other leading ob/gyns and experts in abortion are preparing or have prepared comprehensive training materials in many forms, including print, video, website, and interactive case studies on CD ROM. Such materials have already been used at training sessions and will be available to physicians on

[2]See DEA Form 224, Application for Registration under Controlled Substances Act, Item 4, which requires the applicant to provide a State license number and, if applicable, a State Controlled Substances Number, but does not require submission of a copy of either license.

request from Danco, NAF, and other sources. Physicians who obtain their training from the NAF programs, the CD ROM, the web site, or the self study guide will receive CME credit, which is a further inducement for them to participate.

In light of the ready availability on request of a wide variety of self-instruction materials and frequent training programs in locations around the country, and with so many of the training programs and self-instruction materials the subject of CME credit, physicians will find it easy to obtain the information they need about every aspect of mifepristone. We also want to note that the mifepristone protocol is quite straightforward and the drug's sequelae are predictable, making the physicians' task of mastering the necessary information easier than is the case for more complicated regimens.

In addition, we want to remind you that Danco has established a group of experts in mifepristone who will be available to prescribers via an 800 number on a 24 hours per day 7 days a week basis for at least one year post-approval.[3] The availability of knowledgeable experts to provide consults on an immediate basis provides an additional layer of reassurance.

We think the training materials and programs already or soon to be available are quite extensive in light of the relative simplicity of the mifepristone protocol, and we therefore believe they are more than adequate to achieve the goal of prescriber knowledge. The question FDA has raised is whether it is also necessary to have certification of each prescriber's completion of a particular program, the curriculum of which is approved by FDA. We do not believe that this is necessary or appropriate. Although FDA sometimes requires and sponsors sometimes propose such certification for medical devices for which "hands-on" training on animals or even humans is necessary to attain proficiency in use of the device, it is rare - indeed, we think, unheard of - where it is cognitive rather than hands-on knowledge that the prescriber needs.

We think the same logic applies to the question of whether the prescriber should have to provide certification of his/her training in and ability to diagnose accurately the age of the pregnancy and whether there is an ectopic pregnancy. By signing the Prescriber's Letter, the physician is stating that she or he has the ability to do so, and because these are basic skills for physicians, including those most likely to

[3] This program is discussed on page 19 of the Distribution Plan under the heading "On-Call Regional Medical Consultants."

prescribe mifepristone (obstetrics/gynecology, family practice, and general practice), we see no reason to doubt the physician's statement.

We also think it is important to note that failure to assess the duration of the pregnancy with absolute precision is not an issue. For example, if the physician thinks the pregnancy is at 49 days but the pregnancy is actually of shorter duration, then prescribing mifepristone will still be within the labeled indication. If the physician concludes that the duration of the pregnancy is 49 days or less but it actually exceeds 49 days by a week or two, that may reduce the efficacy, but will not alter the safety of the drug. Thus, while precision is certainly desirable, some inaccuracy is tolerable from a safety and efficacy standpoint. Similarly, we think FDA should recognize that although mifepristone is ineffective in terminating an ectopic pregnancy, the drug will not change the course or the outcome of an ectopic pregnancy. A physician's failure to make this diagnosis accurately, as could also occur with a patient seeking to carry to term or one seeking a surgical abortion, actually has nothing to do with mifepristone. None of this is to say that we or FDA should seek anything less than excellence in prescribers and their diagnoses of the duration of intra-uterine pregnancy and ectopic pregnancy before prescribing mifepristone; it is only to say that the risks of any such inaccuracy are not so great as to warrant doubting the word of practitioners or requiring certification of their ability to perform these tasks.

FDA has also proposed requiring practitioners to have the ability to conduct ultrasound to evaluate the duration of pregnancy, and to have their ability to do so certified. We believe such an ultrasound requirement represents an inappropriate extension of the conditions of the clinical trials into the routine practice of medicine. In the clinical trials, ultrasound was used to provide the maximum amount of information and the most accurate information about the use of mifepristone at different gestational ages. But ultrasound is not routinely used for assessing the duration of intra-uterine pregnancies, and there is no clinical or medical reason for its routine use.[4] Moreover, as noted above, diagnosing the duration of pregnancies without ultrasound is accurate enough for use of mifepristone to have an ample margin of safety. We also want to emphasize that many of the practitioners who would

[4]Although ultrasound is used when ectopic pregnancy is at issue, the incidence of ectopic pregancy is small (estimates range from 1 in 100 to 1 in 200 pregnancies). Because of its rarity, and the fact that mifepristone is not a safety issue in suspected or actual ectopic pregnancy, we do not think the use of ultrasound in ectopic pregnancies should drive regulatory decisions for intra-uterine pregnancies.

consider prescribing mifepristone for medical abortion do not have (because they do not need) training, much less certification, in ultrasound equipment, nor do they have ultrasound in their offices or clinics. Even practitioners who do use ultrasound, frequently refer their patients to ultrasound facilities rather than performing the test themselves. Thus, imposing an ultrasound requirement would significantly but unnecessarily limit the number of practitioners who could prescribe mifepristone, and therefore significantly limit women's access to the option of a medical abortion with mifepristone.

Essentially the same principles apply to the question of whether practitioners need to be qualified in use of ultrasound (or certified in its use) in connection with diagnosis of incomplete abortion. Practitioners assess the presence of incomplete abortion by physical findings and symptoms, and this approach works quite well whether the incomplete abortion is occasioned by mifepristone or is spontaneous. Similarly, on-going pregnancy is assessed by physical examination, signs (including absence of bleeding), and pregnancy tests. Because incomplete abortion and on-going pregnancy are managed effectively without it, ultrasound is unnecessary and should not be required.

We think such a requirement is wholly inappropriate. Specialization is a fact of life in modern American medical practice, and it is absolutely routine for physicians to refer patients to one or more other physicians for various aspects of their care. Such referrals can occur at any time in the clinical course of a disease or condition; they are sometimes made at the outset of a patient's care, sometimes during the course of a patient's care for a second opinion or more extensive involvement by another doctor, and sometimes on an emergent basis when the original provider needs help or the patient is away from the original provider's location. There is no reason at all for mifepristone to be one of the very few exceptions to these common practices, and there are at least two very important reasons for it not to be.

The first is that no more than 5 - 8% of all patients who take mifepristone require surgical aspiration curettage. (Only 1% have an on-going pregnancy, and urgent surgical intervention is not required for this group of patients.) Thus, requiring that all physicians involved in the mifepristone protocol be able to provide such a service is disproportionate to the need. Second, the number of

physicians willing to perform surgical abortions is, for a variety of reasons, decreasing, and those who do perform them have sound reasons not to identify themselves unnecessarily. For that reason, any such FDA requirement is, literally, a restriction of mifepristone to those physicians who already do surgical abortions, and thus literally a nullification of the expansion of options that mifepristone is intended to provide.

For all these reasons, it should be enough for the package insert and the prescriber letter to advise physicians, as they do, that the patient may need care for incomplete abortion, and leave it to the physician, as part of the practice of medicine and in the exercise of his or her professional judgment, to decide when and by whom such care will be provided, just as is now done for the sequelae of other medical conditions, drugs, and medical devices.

The same is true for the care of women in case of need of resuscitation or blood transfusions. We note again, as we did above, that the need for such care is expected to be extremely rare, and we also note that the need for resuscitation or blood transfusions is not peculiar to mifepristone; it arises in the case of miscarriages as well as in the case of numerous non-pregnancy related illnesses and conditions occurring in both women and men. The American health care system provides such care, when needed, in a variety of different ways, and it is not always provided by the patient's regular or original physician. Accordingly, what the mifepristone prescriber needs is not necessarily admitting privileges at a nearby hospital (much less certification of such privileges) but rather complete and clear information about the patient's likely course that will allow her or him to consider the available options in the event of emergent occurrences and work with the patient as her professional and involved guide to the health care system. Both the package insert and the training materials will provide exactly that information; the rest should be left to the physician as part of the practice of medicine and in the exercise of his or her professional judgment.[5] Nor is there any need for the prescriber to be within one hour of any particular treatment

[5]As noted above, experts in medical abortion with mifepristone will be available to provide consults on a 24/7 basis. These consults can help inform the prescriber's own judgments.

facility. As noted above, further care, if needed, will be provided as part of the health care system, and the prescriber need not be geographically proximate to any particular facility for the patient to receive the necessary care.

In summary, we intend to carry out fully our commitments to provide information, training, and expert assistance to physicians who prescribe mifepristone, and we intend to carry out fully our commitments to provide, via their physicians, written information to patients considering medical abortion with mifepristone. We believe that with that information and training and the help of readily available expert assistance, if needed, and in light of the safety and efficacy of mifepristone and the predictability of the course of patients who take it, physicians will be able to manage successfully the care of patients who choose medical abortions with mifepristone. To require additional layers of regulation is unnecessary and therefore inappropriate, and also unfortunately likely to limit access to this important new drug.

* * *

FDA's minutes of our June 1 telephone call also discuss questions other than distribution questions, such as Phase IV commitments, the applicability of Subpart H, and labeling recommendations. As to Phase IV, we reiterate our intention to submit proposed protocols before August 1. With respect to Subpart H, we continue to believe that it is impermissible for FDA to apply this provision to mifepristone, because the drug is not intended for use in either serious or life-threatening conditions. Nor do we want to have use of this important drug discouraged by branding it as a Subpart H drug. A copy of our previous comments on this issue is attached.

As to the labeling recommendations briefly noted in the minutes, we look forward to working with you on revisions to simplify the labeling and make it more effective for the clinician to use. We have received FDA's comments on and information requests about the draft labeling, and will, as requested, respond promptly in writing.

We especially want to reiterate our appreciation for your sending us comments, proposals, and drafts at the earliest possible time and also our commitment to work as hard as we can to reach agreement with you on the remaining issues, so that FDA can announce its approval of mifepristone as soon as possible.

Very truly yours,

Sandra P. Arnold

Sandra P. Arnold

Attachments:
- Distribution Plan for Mifeprix, Amendment 039
- Comments regarding Subpart H

cc: Nancy L. Buc, Esq. – Buc & Beardsley

Frederick H. Schmidt – Population Council

Patricia Vaughan, Esq. – Population Council

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
One Dag Hammarskjold Plaza
New York, NY 10017

JUN 23 2000

Dear Ms. Arnold:

We acknowledge your June 12, 2000 request for a meeting to discuss the drug review for mifepristone. FDA categorizes meetings into three types:

Type A: A meeting that is necessary for an otherwise stalled drug development program to proceed.
Type B: A meeting described under drug regulations (e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2/Pre-Phase 3, Pre NDA).
Type C: All meetings other than those that qualify for Type A or B.

Based on the purpose, objectives, and proposed agenda, we consider the meeting to be a Type C. This meeting has been scheduled for:

Date:	July 19, 2000
Time:	9:00 am
Location:	Parklawn Building, Conference Center, Room "Potomac"
CDER participants:	[redacted]

The background information for this meeting should be received by the Agency at least 2 weeks prior to the meeting. If we do not receive it by July 5, 2000, rescheduling of the meeting may be necessary.

If you have any questions, contact the undersigned at [redacted]

Sincerely,

/S/ 6/21/00

[redacted]
Project Management Staff
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ORIGINAL

NATIONAL ABORTION FEDERATION

June 22, 2000

Food and Drug Administration
HFI-40
Rockville, MD 20857

Dear [redacted]

Yesterday, we were contacted by [redacted] for information regarding state "physician-only" laws for abortion. Although she had a list of states with physician-only laws, this information alone cannot definitively guide determinations about the role of non-physician practitioners (i.e. advanced practice clinicians such as nurse practitioners, certified nurse midwives, and physician assistants) in providing abortion care. To clarify, we would like to offer you background about physician-only laws and an explanation of other regulations and statutes, specifically those related to the prescriptive authority and scope of practice of advanced practice clinicians, that must be considered in drawing conclusions about which personnel are authorized to provide abortion care.

Physician-only laws first became common with the original movement to criminalize abortion in the late 1800s. The anti-abortion campaign of the nineteenth century is understood as a key component of a larger battle, namely, the attempt of "regular" or "elite" university-trained physicians to attain professional dominance over the wide range of "irregular" medical practitioners - homeopaths, apothecaries, dentists, etc. Thus, the objective of elite physicians was to control the terms under which approved abortions could be performed, restricting their provision to physicians operating in hospitals and for medically indicated reasons.

With the liberalization of abortion laws in the 1970s following the 1973 *Roe v. Wade* decision, many states retained the physician-only provisions in their abortion statutes, reasoning that the deaths, sterility, and other complications associated with illegal abortions could be prevented if such abortions were performed by competent medical personnel in medical facilities. Because many states' physician-only laws predate the laws and regulations governing the scope of practice of advanced practice clinicians, they do not take into account the professional training and abilities of physician assistants and advanced practice nurses, whose professions came into existence in the late 1970s.

In the intervening decades, the nurse practitioner, certified nurse midwife, and physician assistant professions have matured to encompass a multifaceted role in today's health care system. Advanced practice clinicians perform a variety of procedures that are more complex than surgical abortions, and in most states, they are able to prescribe medications, like narcotics, anti-depressants, and hormones. In many states, physician-only laws are in direct conflict with the professional practice acts and corresponding regulations governing advanced practice clinicians, including scope of practice and prescriptive authority.

1755 Massachusetts Ave. NW Suite 600 Washington, DC 20036 Telephone: 202.667.5881 Fax: 202.667.5890

Because of the regulatory conflicts that exist, some states have taken steps to resolve the ambiguity and determine which regulations take precedence. In fact, the New York State Department of Health issued a declaratory ruling in 1995 indicating that New York's scope of practice regulations for physician assistants supercedes New York State's physician-only law. Further, the Montana Supreme Court ruled in 1999 that a law barring physician assistants from providing abortions was unconstitutional. This year, the Rhode Island Department of Health amended their termination of pregnancy regulations to authorize advanced practice clinicians to provide medical abortion. These are clear examples of the many statutes, regulations, and rulings that together determine the role of advanced practice clinicians on the state level.

To further illuminate the complexity of this issue, we have enclosed relevant portions of two very recent journal articles. The first was published last month in a supplement to the *Journal of the American Medical Women's Association* and includes a discussion of physician-only laws as they pertain to medical abortion. The second is currently in press at the *American Journal of Obstetrics and Gynecology*. We hope that you find these materials helpful. If we can be of any further assistance, please call us at (202) 667-5881.

Sincerely,

Susan Dudley

Susan D. Dudley, PhD
Deputy Director

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

June 22, 2000

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

BC

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

- Amendment 048 - Drug Substance Chemistry, Manufacturing and Controls (CMC) Section Update

Dear ———:

This Amendment 048 provides an update to the Drug Substance CMC originally filed as Amendment 025 on June 3, 1999 and subsequently revised by Amendments 028 (June 30, 1999), 037 (November 29, 1999), 040 (January 28, 2000) and 043 (March 30, 2000).

This update to the CMC incorporates several validated process adjustments implemented by the manufacturer, as well as other minor changes. Set forth below is a brief synopsis of the updated information.

A. Validated Process Adjustments

Several adjustments were implemented by the manufacturer so that (1) the commercial mifepristone manufacturing process adheres more closely to the Roussel process in terms of auxiliary material charges, and (2) material transfer at various stages in the manufacturing operation is enhanced.

These process adjustments are presented and described in Attachment A-1 organized by process step. Attachment A-1 also includes a brief explanation of the reason for the change, as well as page number references to the affected pages within the current CMC. Replacement pages to the CMC are provided in Attachment A-2.

These changes were initially developed and evaluated at laboratory scale (see Attachment A-3, Laboratory Scale Validation Protocol and Report) and were subsequently validated in a [redacted] batch plant scale manufacturing campaign. (see Attachment A-4, Plant Scale Validation Protocol and Report). The results of the process validation showed that the mifepristone manufacturing process performed consistently and within specification, and resulted in mifepristone that was comparable to the mifepristone produced during the initial validation campaign. Additionally, samples of mifepristone from the adjusted process were tested [redacted]

All of the process changes were documented in accordance with the factory's change control procedures and approved for routine production on October 17, 1999. Since that time, approximately [redacted] production batches have been successfully made by the manufacturer using the adjusted process, further demonstrating the consistency of the adjusted process.

B. Other Corrections

The other minor corrections consist of the following: (1) changes that were implemented based upon observations and recommendations that resulted from the original process validation effort (See Attachment B-1) and (2) typographical corrections (See Attachment B-2). Please note that Attachments B-1 and B-2 both include brief explanations of the changes, as well as page number references to the affected pages within the current CMC. We also are providing the relevant replacement pages for the CMC in Attachment B-3.

For ease of reference, we are enclosing as Attachment C, the original CMC for the Drug Substance revised to include this amendment as well as all prior amendments. This revised CMC represents the process as it has been followed by the manufacturer since late fall of 1999.

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

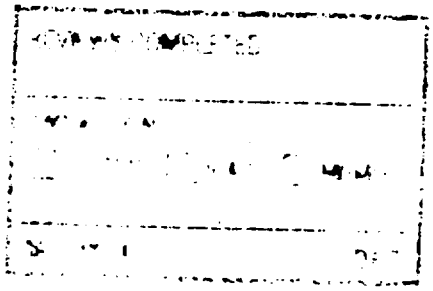
Sincerely,

[redacted]

President and Chief Executive Officer

Enclosures

cc: Sandra P. Arnold – Population Council
[redacted] – FDA
Nancy L. Buc, Esq. – Buc & Beardsley
[redacted]
Frederick H. Schmidt – Population Council



TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA

COMMITTEE ON COMMERCE
SUBCOMMITTEES:
HEALTH AND ENVIRONMENT
ENERGY AND POWER

Congress of the United States
House of Representatives
Washington, DC 20515–3602

215 STATE STREET, SUITE 815
MUSKOGEE, OK 74401
(918) 687-2533
(918) 682-8503 (FAX)

120 S. MISSOURI, ROOM 105
CLAREMORE, OK 74017
(918) 341-9336
(918) 341-9437 (FAX)

34 "A" STREET N.E., ROOM 202
MIAMI, OK 74354
(918) 542-5337
(918) 542-5367 (FAX)

June 16, 2000

The Honorable Donna E. Shalala
Secretary
Department of Health and Humans Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Shalala,

It is my understanding that the Food and Drug Administration is poised to appoint Susan Allen, an individual who once headed the mifepristone marketing and training program, as head of the division overseeing the abortifacient's release. This is a cause of great concern. Even if she were to recuse herself from any discussions of the drug's final approval, the conflict of interest involved in her administering the division which would monitor distribution, review safety, and conduct post-marketing of mifepristone is sufficient to compromise the public's trust in the objectivity and integrity of the FDA and its determinations with regard to the safety and effectiveness of this drug and its protocol.

Mifepristone's U.S. sponsor, the Population Council of New York, set up a company called "Advances in Health Technology" sometime in or around 1996, to promote the drug and provide public education and handle doctor training. Susan Allen, M.D., a doctor who admits to providing "thousands of abortions" in the United States, was appointed the company's first president and CEO and argued for the group's controversial training program before the FDA advisory panel that met to consider the marketing application for mifepristone in July of 1996.

When Allen proposed to that committee that physicians with no previous surgical abortion training or experience would be trained to date pregnancies, manage complications, and perform surgical abortions as a back up for failed chemical abortions in brief seminars, panelists were appalled.

FDA guest-speaker Richard Azziz, M.D., M.P.H., professor of obstetrics and gynecology at the University of Alabama at Birmingham, told Allen he thought they were "treading on very dangerous ground." He called the plan to "train nonsurgeons to do a procedure which is a D&C on a pregnant uterus" an "error" and "extremely risky."

Committee member Vivian Lewis, M.D. told Allen that she agreed with Azziz. "I do not think you can teach somebody to do a surgical evacuation of the uterus in a simple seminar with a mannequin or something." Panelist Cassandra E. Henderson, M.D., said, "I think you can. You just cannot handle the complications."

429 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701 Fax: (202) 225-3038

E-mail: rep.coburn@mail.house.gov
Web site: www.house.gov/coburn

Lewis told Allen that "if you are talking about in an emergency situation having the skill to be able to do this deftly, appropriately, and with minimal complication, such a person who has never been trained in that and who has only attended a seminar is the worst possible choice of person to do that."

After hearing the discussion between Allen and various panelists, committee chair Ezra C. Davidson, M.D. summarized the panel's reaction for the FDA by saying, "I think what you are hearing from the committee [in regard to] the issue of skills being discussed, [is that] there is considerable unease about how that certification and documentation is going to be done to ensure safe delivery of this regimen and management of its complications."

Given that the certification of doctors, the identification of surgical backup, and the tracking and management of complications are, if press accounts are accurate, measures now being proposed by the FDA to help "ensure the safe delivery of this regimen and management of its complications," putting Allen, someone who never admitted the need for such safeguards, in charge of the division which would oversee their implementation smacks too much of the situation of having the foxes guard the henhouse. Even if the sponsor agrees to such monitoring, what assurance would the American public have that such safeguards would be enforced?

If nothing else, Dr. Allen's previous cozy relationship with the sponsor of this controversial pill should itself be reason to question the wisdom of such an appointment. Should the sponsor of a drug and the head of a division overseeing the marketing application of such a drug ever be that close? What confidence can the American consumer have in a drug's safety when the FDA puts the sponsor's former licensee in charge of decisions about the release of the drug, or monitoring of the drug, or releasing information about the drug's safety?

I would appreciate prompt answers to the following questions:

1) Who made the decision to hire Susan Allen?

2) Who made the decision to put Susan Allen in charge of the FDA's Reproductive and Urologic Drug Products Division?

3) What role will the FDA's Reproductive and Urologic Drug Products Division have in determining the final approval/disapproval of the marketing application for mifepristone?

4) What role will the Reproductive and Urologic Drug Products Division have in monitoring the distribution of mifepristone, the qualifications of doctors prescribing mifepristone, the conditions under which mifepristone is used, and the condition of the women who take mifepristone, the reporting of complications and the ability of doctors to handle complications associated with mifepristone?

5) How aware are the FDA and HHS of the inherent conflict of interest involved in the hiring and promotion of Susan Allen and its ramifications for the confidence and safety of

women taking mifepristone?

Thank you for your prompt attention to this matter. I look forward to a timely response.

Sincerely,

Tom A. Coburn, M.D.
Vice Chairman
Commerce Subcommittee on
Health and Environment

APPEARS THIS WAY
ON ORIGINAL

National Association of Pediatric Nurse Associates & Practitioners, Inc.

|S| 6/30/00

June 9, 2000

Honorable Jane E. Henney, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Commissioner Henney:

I'm writing on behalf of the National Association of Pediatric Nurse Associates and Practitioners (NAPNAP), representing 5,800 Pediatric Nurse Practitioners (PNPs) nationwide. We understand there is a story in yesterday's New York Times which reports that the U.S. Food and Drug Administration (FDA) is considering a provision that would require "doctors" to register to prescribe a new drug, and that the proposal uses the word "physician" rather than "health care provider." NAPNAP believes that use of only the term physician is not only discriminatory, but is also inconsistent with the position articulated by the Agency that it avoids involvement in issues regarding the scope of practice of health care providers which includes prescribing privileges.

We urge the FDA to use the term of art "health care provider" rather than "physician" when referring to health care professionals with prescribing privileges in not only the policy under consideration, but also in all future regulations, proposals, guidance documents, or other advisory materials. The states determine the qualifications and related scope of practice for health care providers through state licensure laws. All fifty states recognize nurse practitioners and every state, including the District of Columbia, grants NPs some degree of prescriptive authority. By using the term physician exclusively, the FDA ignores this fact, and that over 71,000 NPs assist in meeting the health care needs of this country.

This issue has been raised with the FDA on several previous occasions in relation to the FDA's direct-to-consumer advertising guidance and over-the-counter product labeling rule. The Agency specifically acknowledges in your Consumer Advertising Guidance Q&A document that health care providers other than physicians prescribe. If reported correctly by the New York Times, the current proposal would seem to fly in the face of the FDA's own positions in these matters.

Again, NAPNAP urges the FDA to reassess this proposal. We thank you for your consideration of this letter and look forward to your reply.

Sincerely,

Robert A. Hall, MEd
Executive Director

CC: _____

_____

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

00-4056

1101 Kings Highway, North, Suite 206 / Cherry Hill, New Jersey 08034-1912
E-mail: napnap1@aol.com Internet: www.napnap.org
856-667-1773 / Toll Free: 877-662-7627 / FAX 856-667-7187

Abortion Provision in the U.S.

[redacted], DRUDP

June 14, 2000

Number of abortions

1.37 million abortions were performed in the U.S. in 1996 (50 million worldwide, 20 million legal)

Procedures

- 98% by D&C
- 2,988 medical procedures were reported to CDC in 1997
- 4,200 medical abortions were reported to AGI in 1996, and 4,300 in 1st half of 1997, using mifepristone or off-label methotrexate. (AGI data is believed to be more complete than CDC data)
- According to NAF, for medical abortions, the misoprostol is taken at home.

Cost (1997)

Nonhospital facilities, surgical abortion at 10 wk gestation with local anesthesia, $150-$1535 (Average $316)
Medical abortion costs $100-$1250, average $401.

Demographics

- 2% of women ages 15-44 have abortions each year.
- 43% of women have at least 1 abortion by age 45
- 60% of abortions are provided to white women, BUT blacks are 3 times as likely and hispanics are 2 times as likely to have an abortion.

Gestational ages

- 88% of abortions are performed in 1st 12 weeks gestation
- 55% up to 8 weeks
- 36% up to 7 weeks (49 days)
- 43% of abortion facilities provide abortions only through 12 weeks gestation
- 42% of nonhospital facilities provided abortions under 6 weeks gestation in 1996, compared to 33% in 1992

Facilities

- 90% of abortions are performed in clinics
- 3% of abortions are performed in doctor's offices
- 7% of abortions are performed in hospitals
- 42% of nonhospital facilities provide abortion to women less than 6 weeks gestation
- 24 hour emergency contact must be readily available.
- NAF established guidelines for members

Providers

- Forty four states and the District of Columbia have statutes or regulations that prohibit anyone other than a licensed physician from performing an abortion. Only six states (AZ, KS, NH, OR, VT, WV) do not have laws limiting the performance of abortions to physicians.
- Not all physician-only laws prevent non-physician practitioners from performing medical abortions. In rare instances, physician-only laws may not apply to medical abortion because they employ a relatively narrow definition of abortion. (See attached facsimile from National Abortion Federation, pages A-K).
  - HI defines "abortion" as "an operation to intentionally terminate the pregnancy of a nonviable fetus"; RI forbids non-physicians to perform surgical abortion, but not medical abortions; NY's Dept. of Health ruled that physician assistants (PAs) may perform abortions under NY law; MT struck down statutory provisions prohibiting PAs from performing abortions. (Both NY and MT rulings are applicable to medical abortions.)
- The number of abortion providers in the U.S. decreased by 14% (from 2380 to 2042) from 1992 to 1996

Complications of spontaneous abortions

Although spontaneous abortions are known to be complicated by hemorrhage, infection, and surgical intervention, the available texts do not provide information on the incidence of such complications, and focus instead on the etiologies and management of spontaneous abortion, and recurrent pregnancy loss.

References

The Henry J. Kaiser Family Foundation at http://www.kff.org/
The Alan Guttmacher Institute at http://www.agi-usa.org/pubs/fb_induced_abortion.html

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Parklawn Building, Room 17B-45
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date:** June 1, 2000

To: [redacted]

Fax Number: [redacted] **Voice Number:** [redacted]

From: [redacted]

Fax Number: [redacted] **Voice Number:** [redacted]

Message: Proposed Restricted Distribution System for NDA 20-687

Please note that we do not consider this a formal communication.

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

THIS DOCUMENT IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.
Thank you.

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

May 17, 2000

ORIGINAL

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

BC

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

- Amendment 047 - Additional Information on ——— Impurity Profile for Roussel Drug Product and Danco Stability Commitment

Dear ———

This Amendment 047 provides information requested in the FDA Teleconference Minutes dated April 25, 2000 concerning:

1) The commitment to develop ——— of Drug Substance (See Attachment A)

2) The revised ——— of Roussel Drug Product which establish a link to Danco Drug Product to allow for — month initial expiry dating of the Danco Drug Product (See Attachment B)

3) The revision in the stability commitment to include the use of long-term data collected on the Danco pre-approval Drug Product batches for post-approval extension of the expiry dating for Danco Drug Product (See Attachment C).

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

Sincerely,

/S/

President and Chief Executive Officer

REVIEWS COMPLETED

CMC ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

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
Enclosures

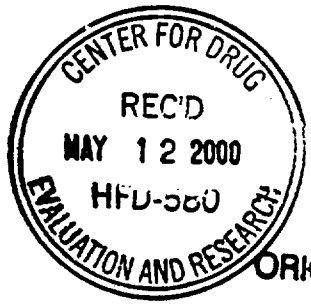
cc: Sandra P. Arnold – Population Council
[redacted] - FDA
Nancy L. Buc, Esq. – Buc & Beardsley
[redacted]
Frederick H. Schmidt – Population Council
[redacted]
Patricia C. Vaughan, Esq. – Population Council

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

May 11, 2000

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

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 046 - Methods Validation Package Supplement

Dear

This Amendment 046 contains five copies of the Certificate of Analysis for the Drug Substance working reference standard not included in Amendment 045, the Methods Validation package submitted May 3, 2000.

Please insert one of the enclosed Certificate of Analysis copies into each of the five copies of Amendment 045 behind the tab labeled "HuaLian Ref. Standard" and remove the blank page entitled "This Page Will Be Inserted When the Data Is Available".

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

Sincerely

/s/

Enclosures
cc: Sandra P. Arnold – Population Council
– FDA
Nancy L. Buc, Esq. – Buc & Beardsley

Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

Danco Laboratories, LLC

May 3, 2000

ORIGINAL

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

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 045 - Methods Validation Package

Dear ———

This Amendment 045 contains the Methods Validation Package requested by ——— in a guidance teleconference held on April 26 and confirmed in the FDA minutes of that teleconference.

All requested information has been included with the exception of the certificate of analysis for the reference standard from the drug substance manufacturer. This document will be forwarded to the FDA as soon as we receive it from China. Additionally, please note that we have used the only available drug substance manufactured by Roussel as the Roussel reference standard.

We await ——— instructions for shipping the samples of drug substance, impurity and drug product to the designated laboratories. Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

———
President and Chief Executive Officer

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Population Council
Attention: Sandra P. Arnold
1230 York Avenue
New York, NY 10021

APR 25 2000

Dear Ms. Arnold:

We acknowledge receipt on March 31, 2000 of your March 30, 2000 resubmission to your new drug application (NDA) for mifepristone, 600 mg.

This resubmission contains additional chemistry and clinical information submitted in response to our February 18, 2000 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is September 30, 2000.

If you have any questions, call ——————Regulatory Project Manager, at ————

Sincerely,

/S/ 4/25/00

——, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

April 20, 2000

ORIG AMENDMENT

13C

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 044 - Submission of Updated and Additional Stability Data

Dear ———

In our response (Amendment 043 dated March 30, 2000) to Drug Product Comment #2 of the Approvable Letter dated February 18, 2000, we indicated that in April we would have additional stability data on the two Danco Drug Product batches produced:

- Six-month accelerated and six-month long-term on the second Drug Production Batch, Lot #99007, and
- Nine-month long-term on the first Drug Production Batch, Lot #99005.

These new data are enclosed as Attachment 1 together with copies of prior stability data on the same batches for your reference. In addition, we have updated with the new data, the graphs originally presented in our Amendment 040 comparing the stability data for our Drug Product to Roussel Drug Product. These graphs are enclosed as Attachment 2. Danco produced Drug Product continues to demonstrate good stability and the results remain comparable to the original Roussel Drug Product. These data further support our proposal for a — month initial expiry date as requested in our previous response to Drug Product Comment #2, which is enclosed as Attachment 3 herein for your reference.

Drug Product point #10 of the December 14, 1999 FDA Information Request Letter stated that "It is recommended that the ——— of mifepristone be monitored during stability testing". In our response to that point in Amendment 040 dated January

28, 2000 we indicated that the ——————— would be performed on the six-months accelerated storage samples of the first three stability batches.

We have now completed the ——————— studies on the first two Drug Product Batches, Lot #'s 99005 and 99007, and the results are enclosed as Attachment 4. They confirm that the ——————— is solely for ——————— This reaffirms the stability of this product and its ——— form even under the stress conditions of 40°C and 60% humidity for six months. We will provide the ——————— results for the third Drug Product batch in due course.

For your reference, we are enclosing relevant portions of prior submissions on stability as Attachment 5.

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: Sandra P. Arnold – Population Council
Nancy L. Buc, Esq. – Buc & Beardsley
——————————————————
——————— – FDA
——————————————————
Frederick H. Schmidt – Population Council
——————————————————
Patricia C. Vaughan, Esq. – Population Council

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Danco Laboratories, LLC

April 12, 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
- Disk of Labeling from Amendment #043, dated March 30, 2000

Dear ———

Per your request, I am enclosing a disk of the mifepristone labeling, which was submitted as part of Amendment #043, dated March 30, 2000. The disk contains both the clean and marked-up versions of the label.

Please let me know if you have any questions.

Sincerely,

/S/

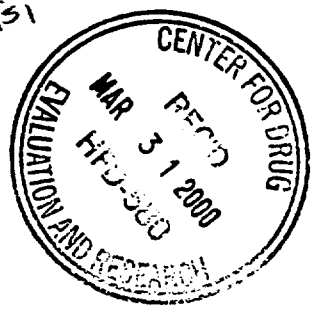
President and Chief Executive Officer

/dns
Enclosure

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

Nancy L. Buc – Buc & Beardsley

Noted
3/31/00
JSL



ORIG AMENDMENT

B2

NDA 20-687
Mifepristone Tablets, 200 mg

International Product Labeling with English Translations

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

Population Council
New York, New York 10017

~~ORIG AMENDMENT~~

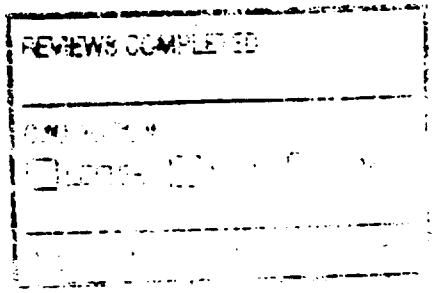
SU

NDA 20-687

Mifepristone Tablets, 200 mg

Safety Update Report #3
July 1, 1999 – February 29, 2000

APPEARS THIS WAY
ON ORIGINAL

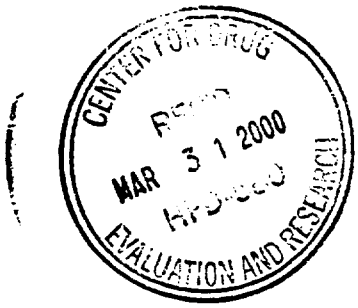


Population Council
New York, New York 10017

The Danco Group

March 30, 2000

noted
3/31/00
/S/



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,

/S/

President and Chief Executive Officer

REVIEWS COMPLETED

/dns
Enclosures

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

——— - FDA
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 ———

Population Council

noted 3/20/00 151

CENTER FOR DRUG REC'D MAR 15 2000 HFD-580 EVALUATION AND RESEARCH

Sandra P. Arnold
Vice President
Corporate Affairs

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

APPEARS THIS WAY
ON ORIGINAL

cc: Nancy L. Buc, Esq.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

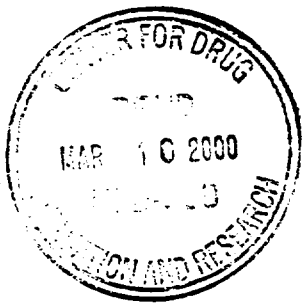
CSO INITIALS /S/ DATE 3/15/00

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

NK

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 ———

Dear ———

As discussed today, given that ——— is no longer ——— the Division of Reproductive and Urologic Drug Products, I would very much like to have the opportunity to have a teleconference with ——— as she is 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,

/S1

———

President and Chief Executive Officer

/dns

cc: Sandra P. Arnold

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE 3/10/00

Danco Laboratories, LLC

March 6, 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

ORIGINAL

NC

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

Dear ———

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

Thank you.

Sincerely,

/S/

mailed
/S/
3/12/00

President and Chief Executive Officer

/dns
Enclosure

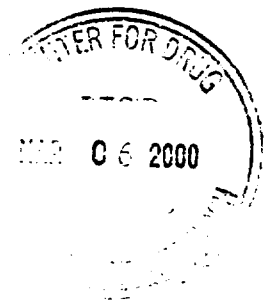
Cc: ——— – FDA
——— – FDA
——— – FDA
Sandra P. Arnold – Population Council

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS /S/ DATE 3/12/00

Danco Laboratories, LLC

March 3, 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

mailed 1:51 3/12/00

NC

NEW CORRES

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 least — substances at — plants, with — plants being successfully audited in 1999 and —— in 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 ——— Compliance Officer, Foreign Inspection Team, who

confirmed that translations are not required as long as an interpreter is provided. ——— 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,

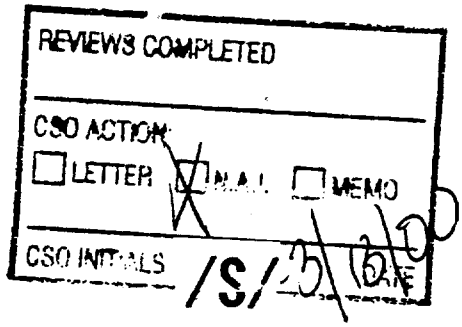
/S/

President and Chief Executive Officer

/dns
Enclosure

Cc: ——— - FDA
——— - FDA
——— - FDA
Sandra P. Arnold – Population Council

APPEARS THIS WAY
ON ORIGINAL



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

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 ———— Regulatory 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

APPEARS THIS WAY
ON ORIGINAL

Enclosure

cc: ———— DRUDP
———— , DRUDP

Frederick Schmidt, Population Council

REVIEWS COMPLETED
CSO INITIALS
☐ LETTER ☐ MEMO
/S/ 25 DATE

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration

7520 Standish Place, HFD-45
Rockville, Maryland 20855
Phone 301.594.0020
Fax 301.594.1204

facsimile transmittal

To:	———	**Fax:**	———
From:	———	**Date:**	2/15/00
Re:	NDA 20-687	**Pages:**	5
CC:			

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Notes: Attached are copies of the signed letter for Dr. Mishell and the signed Clinical Inspection Summary.

APPEARS THIS WAY
ON ORIGINAL

21 CFR 314.50(h) Patent Information

(h) Patent Information. The application is required to contain the patent information described under Section 314.53.

Information on each patent which claims the drug or a method of using the drug is provided below. A copy of each patent and a declaration regarding the patent are appended.

Patents Which Claim the Drug or a Method of Using the Drug

1. US Patent No.: 4,301,146
   Expiration Date: July 29, 2000
   Type of Patent: Drug Product Patent
   Name of Patent Owner: G.D. Searle

2. US Patent No.: 4,386,085
   Expiration Date: January 8, 2002
   Type of Patent: Drug Patent
   Name of Patent Owner: The Population Council, Inc.

3. US Patent No.: 4,447,424
   Expiration Date: January 8, 2002
   Type of Patent: Drug Product Patent
   Name of Patent Owner: The Population Council, Inc.

4. US Patent No.: 4,626,531
   Expiration Date: October 12, 2004
   Type of Patent: Drug Product/Method of Use Patent
   Patent Owner's Place of Business in US: Schering Berlin, Inc., 110 E. Hanover Avenue, Cedar Knolls, NJ 07927-2095

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 16 2000

Daniel R. Mishell, M.D.
1240 North Mission Road
Room 2k1
Los Angeles, CA 90033

Dear Dr. Mishell:

Between December 9 and December 14, 1999, ——— representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol #166A) of the investigational drug mifepristone and misoprostol that you conducted for The Population Council. From our evaluation of the inspection report prepared by ———, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We appreciate the cooperation shown ——— during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/ for

———

———

Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

The Danco Group

January 28, 2000

FEB 0 1 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

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

President and Chief Executive Officer

/dns
Enclosure

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

DATE

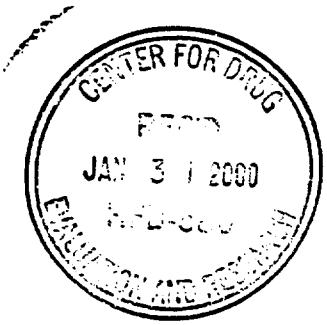
This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc.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

ORIGINAL

The Danco Group

January 28, 2000

ORIG AMENDMENT



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 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

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ MEMO
CSO INITIALS DATE

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

——— · FDA

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 ———

INCOMING CALLS

DATE 1-27-00 NAME _____

TIME	AM PM	NAME	MESSAGE	TIME CALL COMPLETED
vm				
vm				✓
vm				✓
				✓
vm			re: dis. plan	

MIF 001490

The Danco Group

ORIGINAL

January 21, 2000

ORIG AMENDMENT

BC

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.

Sincerely,

[redacted]

President and Chief Executive Officer

/dns
Enclosure

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

cc: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council
[redacted]
[redacted]
[redacted] - FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

580

Food and Drug Administration
Rockville MD 20857

JAN 18 2000

Susan Haskell, M.D.
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314

Dear Dr. Haskell:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 166A) of mifepristone that you conducted for Population Council.

Between November 16 and November 18, 1999, ———— representing the Food and Drug Administration (Agency), inspected the study identified above. From our evaluation of the inspection report prepared by ———— and copies of study records obtained during the inspection, we conclude that you conducted your study in compliance with the Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of the Agency's Bioresearch Monitoring Program This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Investigator ———— during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

————————

————

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

APPEARS THIS WAY

MIF 001493

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 12 1999
2000

Suzanne T. Poppema, M.D.
Aurora Medical Services
1207 N. Street, Suite 214
Seattle, Washington 98133

Dear Dr. Poppema:

Between November 1 and November 5, 1999, ———— representing the Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol #166A) of the investigational drugs mifepristone and misoprostol. You conducted this study for The Population Council, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to the Federal regulations and/or good clinical practices that govern the conduct of clinical studies and the protection of human subjects.

We appreciate the cooperation shown ———, during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

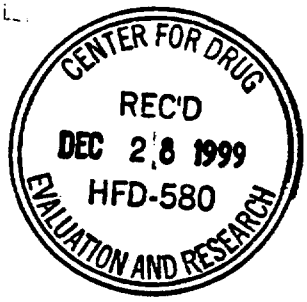
———

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

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

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,

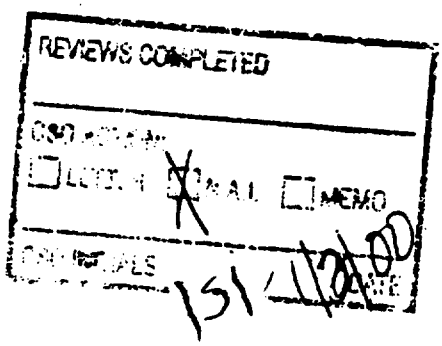
/S/

[redacted]
President and Chief Executive Officer

/dns

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

APPEARS THIS WAY
ON ORIGINAL



NDA 20-687

INFORMATION REQUEST LETTER

Population Council
Attention: Sandra Arnold
Vice President
One Dag Hammarskjold Plaza
New York, NY 10017

DEC 14 1999

Dear Ms. Arnold:

Please refer to the March 14, 1996 new drug application for Mifeprex (mifepristone) tablets, 200 mg.

We also refer to your submissions dated April 28, May 10 and 20, June 3, 15 and 30, July 14 and 22, August 13 and 18, September 13, October 26, November 16 and 29, and December 6 and 7, 1999.

We are reviewing the Biopharmaceutics and Chemistry sections of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Biopharmaceutics

Please provide the comparison of multipoint (5, 10, 20 and 30 minutes) dissolution profiles of the clinical and the to-be-marketed formulations at 50 rpm.

Chemistry

Drug Substance:

ORIGINAL

The Danco Group ORIG AMENDMENT

BC

December 6, 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

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,

/S/

President and
Chief Executive Officer

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

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 ———

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

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

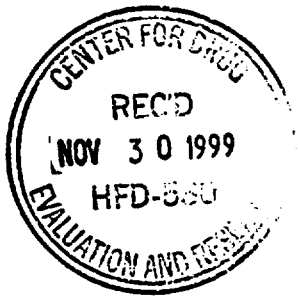
One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

The Danco Group

November 29, 1999

ORIG AMENDMENT
BC

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 037 - Chemistry, Manufacturing and Controls (CMC) Section 1 for Drug Substance: Amendment

Dear ———

This Amendment #037 to the NDA is an amendment to the CMC for our Drug Substance Manufacturer. It includes revisions based upon observations made to Shanghai HuaLian Pharmaceutical Co., Ltd. immediately following their Pre-Approval Inspection (PAI) on October 28, as well as other related revisions which the company felt were also appropriate.

Replacement pages are provided which are cross-referenced to the original Drug Substance CMC filed on June 3 as Amendment #025. Each replacement page has the change(s) highlighted in bold and italics and for your reference, each change is listed by page number in a Revision Summary.

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

Sincerely,

/S/

———
President and
Chief Executive Officer

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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 ———