The Danco Group

January 28, 2000

[redacted]
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

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

Dear [redacted]

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,

/dns
Enclosure

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

[redacted]

REVIEWED
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 [redacted]

The Danco Group

ORIGINAL

January 21, 2000

ORIG AMENDMENT

BC

[redacted]
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 [redacted]

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 mife~~pristone 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,

/s/

/dns
Enclosure

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

cc:

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

ORIGINAL

The Danco Group ORIG AMENDMENT

BC

December 6, 1999

[redacted]
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 [redacted]

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/ [redacted]

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 [redacted]

The Danco Group

December 23, 1999

[redacted]
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 [redacted]

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
[redacted]		[redacted]

[redacted]

[redacted]

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 [redacted]

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,

/dns

cc:

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

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED
CSO
LETTER FINAL MEMO
ORIGINALS /S/ DATE

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/

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

November 29, 1999

ORIG AMENDMENT
BM

VIA FEDERAL EXPRESS

[redacted]
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 [redacted]

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

In reference to our first set of answers to [redacted] 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
[redacted]
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

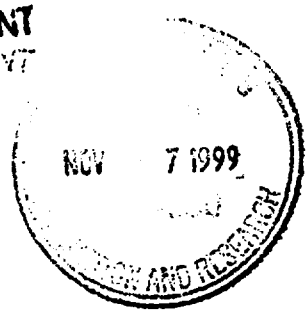
The Danco Group

ORIGINAL

November 16, 1999

ORIG AMENDMENT

BC



[redacted]

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 036 - Supplemental Information to Drug Substance and Drug Product Chemistry, Manufacturing and Controls (CMC) Submissions

Dear [redacted]

We are responding to your request for additional detail regarding the Drug Substance and Drug Product CMC submissions.

1. Certificate of Analysis of Roussel Mifepristone Lot 4V 1014 BJ.

   We are enclosing the Roussel Certificate of analysis for this lot (Attachment 1). This is the lot that has been referred to in the Drug Substance CMC, submitted as Amendments # 025 and #028.

   Following your request, a reanalysis of a sample from this lot is currently underway. We will report those results as soon as they become available The method of analysis used is the same [redacted] method that we have used previously both in China and at the U.S. testing laboratory and that is currently being re-validated in the U.S.

2. Certificates of Analysis for [redacted]

   We are enclosing the certificates of analysis for the [redacted] batches referred to in our Drug Substance CMC, submitted as Amendment #028 (Attachment 2).

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 [redacted]

3. Originals for the [redacted] in the Drug Substance CMC.

   Copies of this data were originally provided in our Drug Substance CMC, submitted as Amendment #025. The source laboratory of these data, [redacted] has reprinted their original data which are enclosed (Attachment 3).

4. Excipient Suppliers' Certificates of Analysis for Drug Product Batch # 99005.

   We are enclosing suppliers' Certificates of Analysis for those excipients that were utilized in the manufacture of Drug Product (Attachment 4). These data were included in the original Drug Product CMC, submitted as Amendment #032 and are provided here again for ease of reference.

5. Environment Assessment for Drug Product and Drug Substance.

   Since the expected introduction concentration (EIC) calculations for the Drug Product produced at [redacted] result in a value of [redacted] parts per billion (ppb) which is less than [redacted] the Tier 0 Criteria are met. (Attachment 5). We therefore request Categorical Exclusion from filing a formal Environment Assessment Section for the Drug Product manufactured at [redacted]

   We are awaiting the appropriate Environmental Compliance certificates for Drug Substance from Shanghai HuaLian Pharmaceutical Corporation. These are expected shortly and we will provide you with the information as soon as possible.

In addition, we are preparing the Methods Validation Packages for Drug Substance and Drug Product. This information will be provided together with samples of Drug Substance and Drug Product as well as a sample of the primary impurity in mifepristone, the [redacted]

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

Sincerely,

/S/

/dns
Enclosures

REVIEWS COMPLETED
CSO
CSO INITIALS DATE

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

[redacted]

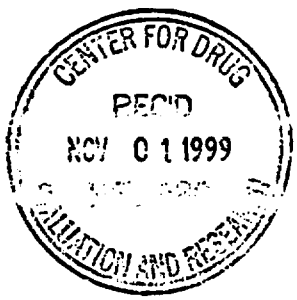
The Danco Group

October 28, 1999

ORIG AMENDMENT

BM

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



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

Dear

In response to your request for additional detail regarding planned distribution of mifepristone if it were subject to Subpart H, Sec. 314.520, we would like to refer you to Amendment 033, point #1 (enclosed).

In that Amendment, we provide a description of the proposed distribution process and in the 4th bullet refer to a letter that would need to be signed by physicians before they could be provided with mifepristone by the distributor.

We are now enclosing the above-mentioned letter for your review and comment.

Please let me know if you have any questions on the information provided.

Sincerely,

/S/

REVIEWS COMPLETED
CSO ACTION:
LETTER MEMO
CSO INITIALS DATE

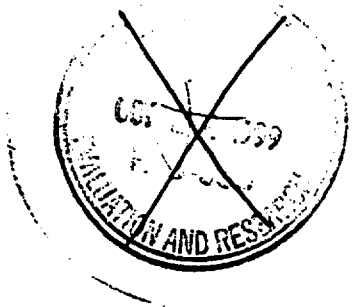
/dns
Enclosure
cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

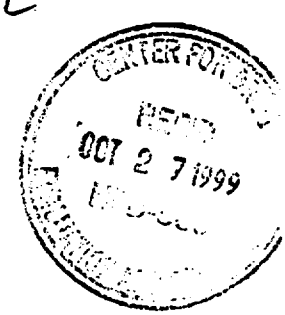
The Danco Group

October 26, 1999

ORIGINAL

ORIG AMENDMENT
BC





[redacted]
Director
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 035 - Danco Produced Drug Product-3 Month Accelerated Stability Data

Dear [redacted]

As a follow up to Danco's commitment to provide the FDA with three (3) month accelerated stability data from the Danco lot 99005 demonstration batch of drug product, we now enclose the data for review by your Division, along with additional supportive data to better frame the expiration period issues.

Pursuant to our prior discussions concerning Danco's efforts to replace the original drug substance and product manufacturer, Roussel Uclaf ("RU"), Danco has secured contract manufacturers who are utilizing the same RU mifepristone synthesis and tabletting processes as described in RU's original CMC submission for NDA No. 20-687. The CMC's for Danco's drug substance and drug product manufacturers have been filed as Amendments 025 and 032, respectively. The enclosed three (3) month accelerated stability data on the Danco mifepristone tablet lot 99005 continues to exhibit acceptable analytical and physical performance. Furthermore, this lot 99005 performs comparably to lots of mifepristone tablets previously manufactured by RU and used in the U.S. clinical studies.

We have enclosed applicable shelf-life and accelerated stability data on various lots of mifepristone tablets produced by both RU and Danco:

A data from the original NDA submission by the Population Council **(RU Stability Data for Mifepristone Tablets)**,

B data from ongoing stability studies of the RU tablet lot [redacted]25524-109) used in the original U.S. clinical studies (**Stability Data for RU Lot [redacted]25524-109**), and

C data from mifepristone tablet demonstration lot 99005 produced by Danco's contract drug product manufacturer using drug substance produced by Danco's drug substance contract manufacturer (**Stability Data for Danco Lot 99005**).

A ***RU Stability Data For Mifepristone Tablets.*** The RU data for blister-packaged mifepristone tablets (stability lots RG 21236-12, RG 21236-44 and RG 21236-50), as originally presented in the NDA (CMC Volume 2 Section B: Drug Product, pages 473-478) are presented in **Attachment A**. The analytical data show that, when stored for sixty (60) months at room temperature (23°C), the tablets continued to perform within specification. Reported assay results fell within the specification range of [redacted]of the product label claim, with no appreciable change being observed in impurity or dissolution performance. The physical test data show that appearance, average mass, disintegration, and hardness also remained consistent throughout the sixty (60) month period. Similar acceptable analytical and physical test data also are observed when tablets are stored at 37°C or 50°C for sixty (60) months, with only minor changes in appearance and [redacted]assay being noted after twenty-four (24) months storage at the 50°C storage condition. All of these data demonstrate that the mifepristone tablet manufacturing process produces a robust and stable drug product.

B ***Stability Data for RU Lot [redacted]25524-109.*** The Population Council, in cooperation with Danco, has continued to perform stability testing of RU tablet lot [redacted]25524-109, which was manufactured in 1994 and used in the U.S. clinical studies. The data collected to date from three (3) separate stability studies conducted on this lot are presented in **Attachment B**. The first series of studies, conducted during 1994 and 1995, included two (2) studies, one controlled room temperature study for twelve (12) months, and one accelerated study (40°C) for twelve (12) months. Another controlled room temperature (25°C/60%RH) stability study which was concluded on May 12, 1999, provides additional data from 1997 to 1999. The analytical data show that assay, impurity, and tablet dissolution performance were acceptable in all three (3) studies throughout the stability test period, indicating that lot [redacted]25524-109 is still maintaining acceptable analytical performance levels fifty-nine (59) months after the date of manufacture.

The tablets for each of the three (3) stability studies described above were stored under bulk storage conditions until they were placed on stability. It should also be noted that the last stability study, the eighteen (18) month controlled room temperature study, was initiated forty (40) months after the date of manufacture of lot [redacted]25524-109. Thus, the data from these studies represent a worst case analysis of anticipated tablet performance. In all instances, including the final time point of the eighteen (18) month controlled room

temperature study, all data were acceptable. These stability testing data further support that the tablet manufacturing process is robust and produces a stable drug product, which could reasonably have an expiration period of [redacted] months, as requested in the original NDA.

C ***Stability Data for Danco Lot 99005.*** In keeping with the stability protocol, demonstration lot 99005 is being stored under room temperature and accelerated conditions. Data after three (3) months storage under accelerated conditions (40°C/75% RH) are presented in **Attachment C**. These data show that, after three (3) months, reported assay data remained within the release specification of [redacted] of the product label claim, and dissolution performance remained well above the specification of [redacted] at [redacted] minutes. Similarly, physical test results show no significant differences or trends.

Summary Data and Comparative Dissolution Profile. In **Table I**, the comparative analytical data from drug product produced by Danco (lot 99005), Roussel Uclaf (lots 29, 30 and 32), and the Population Council's clinical studies material (lot [redacted] 25524-109) are presented to assess their pharmaceutical equivalence. All five (5) lots of drug product were manufactured using the original RU drug substance synthesis and drug product manufacturing process. As shown in **Table I**, there are only minimal differences between the analytical data from the five (5) lots in each of the six (6) specification categories, supporting the conclusion of pharmaceutical equivalence.

Furthermore, the *in vitro* dissolution profiles of the Danco lot 99005 versus RU lot [redacted] 25524-109, previously submitted to FDA in Amendment 032, are equivalent. This data further strengthens the conclusion of equivalence between the Danco manufactured drug product and prior lots manufactured by RU. (**Attachment D**).

Graphs 1, 2, 3, and 4 show graphical presentations of the assay and dissolution data from the stability studies performed, including the on-going stability studies for Danco lot 99005. The data are presented from the zero time point, and extend to the longest testing interval encountered on the studies. These data show that assay data are consistently within the specification of [redacted] of product label claim, and show no downward trend over time. Similarly, the dissolution data are consistently above the release specification of not less than [redacted] released at [redacted] minutes, and show no decline in dissolution rate over time.

All of the data reported for Danco lot 99005 show that tablet performance characteristics are consistent with the characteristics observed in the stability data generated by RU, including the continuing stability data generated on RU lot [redacted] 25524-109. Coincidentally, the RU licensed French manufacturer that is supplying the European market has received a [redacted] expiration period from the European Agency for a drug substance and drug product which, similar to Danco's contract manufacturers, also uses the RU drug substance synthesis and the RU drug product manufacturing process. Based on all the data presented in this amendment, as well as the anticipated data from the ongoing stability study, Danco believes that a [redacted] month expiration period for the Danco drug product is reasonably supported.

APPEARS THIS WAY
ON ORIGINAL

We request that the Division take all of these available data into consideration in making any determination of the expiration period for Danco's mifepristone tablets which we believe should reasonably be for [redacted]

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

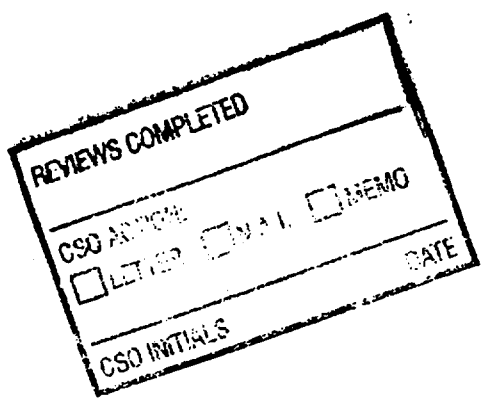
Sincerely,

/S/

/dns
Enclosure

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

APPEARS THIS WAY
ON ORIGINAL

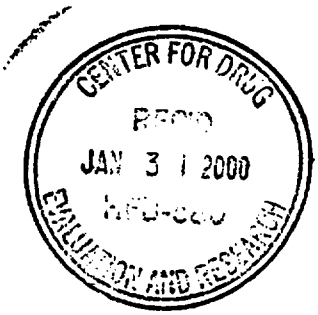


ORIGINAL

The Danco Group

January 28, 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 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/

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

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

Population Council

September 30, 1999

VIA FEDERAL EXPRESS

[redacted]
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
Foreign Labeling

Dear [redacted]

As a follow-up to Dr. Shelley Clark's letter of September 8, 1999, regarding foreign labeling for mifepristone, we are enclosing copies of the following current labels as received from Exelgyn, the French Company:

Appendix 1: Product License and Labeling for France, United Kingdom and Sweden

Appendix 2: Patient Information Leaflets

a. France
b. United Kingdom
   (1) Therapeutic termination of pregnancy between 13 and 20 weeks gestation
   (2) Surgical termination of pregnancy
   (3) Medical termination of pregnancy of up to 63 days gestation
c. Switzerland
d. (Sweden does not require patient leaflets for hospital products.)

Appendix 3: Original English version of European Patient's Information Leaflet translated into various languages

Appendix 4: European Summary of Product Characteristics, 6 July 1999, with cover letter of approval under the Mutual Recognition Procedures of the European Union.

Appendix 5: Copies of box labeling for France and the United Kingdom

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

We have enclosed three (3) sets of the above labels. Please let us know if you need any additional sets of labels.

Sincerely yours,

Frederick H. Schmidt, Ph.D.
Scientist

Enclosures

cc: Sandra P. Arnold
Shelley Clark

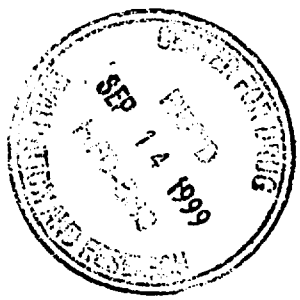
FHS: lm

APPEARS THIS WAY
ON ORIGINAL

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

The Danco Group

September 13, 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
- Amendment 034 - Use of Roussel Uclaf as Reference Standard for Drug Substance

Dear

This Amendment 034 confirms that Danco is utilizing the Roussel Uclaf (not the Gedeon Richter) drug substance and process as the reference standard for manufacture of mifepristone drug substance by the Shanghai HuaLian Pharmaceutical Co., Ltd. All references used and comparisons made in Amendment 025 (CMC for Drug Substance) and Amendment 028 (Supplement to CMC for Drug Substance) are to Roussel Uclaf and not Gedeon Richter.

Please don't hesitate to contact me if you have any questions on this Amendment 034.

Sincerely,

/S/

Chief Executive Officer

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Enclosure

cc:

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

Population Council

NDA 20-687

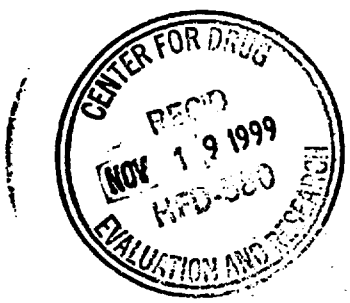
Shelley Clark, Ph.D.
Staff Program Associate
Phone: 212-339-0617
Email: sclark@popcouncil.org

ORIG AMENDMENT

BL

8 September 1999

[redacted]
Food and Drug Administration
Div. of Reproductive and Urologic Drug Products
Room 17B-45, HFD-580
Center for Drug Eval. and Res.
5600 Fishers Lane
Rockville, Maryland 20857



Dear [redacted]

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

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

Sincerely,

Shelley Clark

Shelley Clark, Ph.D.

cc: Sandra Arnold, Population Council

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ [illegible]
CSO INITIALS DATE

Population Council

September 3, 1999

VIA FEDERAL EXPRESS

[redacted]
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 [redacted]

Enclosed please find five (5) copies of Volume 1.1 of our NDA 20-687.

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

Enclosures

cc: Sandra P. Arnold
[redacted]

FHS:as

APPEARS THIS WAY
ON ORIGINAL

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

The Danco Group

ORIGINAL
NEW CORRESP
NC

August 30, 1999

[redacted]
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

Dear [redacted]

We wish to confirm that [redacted] the drug product manufacturer referred to in Amendment 032 of our NDA, will carry out the drug product manufacturing including the final commercial product packaging.

Sincerely,

/S/

Enclosure

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

[redacted]

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Doc1096

The Danco Group

August 18, 1999

[redacted]

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

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

Dear [redacted]

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

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

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

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

Sincerely,

/S/

ORIGINAL

ORIG AMENDMENT

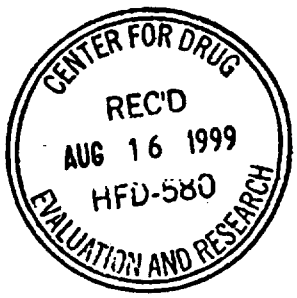
The Danco Group

bc

August 13, 1999

[redacted]

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 032 - Chemistry, Manufacturing and Controls (CMC) Section II for Drug Product

Dear [redacted]

This Amendment 032 is the complete CMC section for our Drug Product.

As agreed during our April 9, 1999 meeting with the FDA, we are filing the CMC section with one-month room temperature stability data and one month accelerated stability data. We will provide three months room temperature and three months accelerated stability data in October. We request that the FDA initiate review of this CMC submission as soon as possible.

Under separate cover a copy of this CMC section has been sent to the attention of [redacted] U.S. Food and Drug Administration District Office.

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

Sincerely,

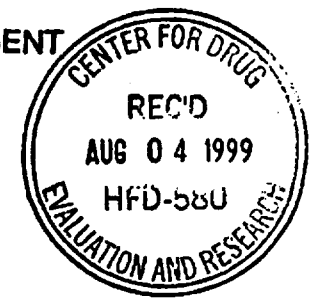
/S/

ORIGINAL

Population Council

ORIG AMENDMENT

SV



Sandra P. Arnold
Vice President
Corporate Affairs

August 3, 1999

VIA FEDERAL EXPRESS

[redacted]

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
Amendment 031 - Additional Response to "FDA Approvable Letter of September 18, 1996"
- Safety Update Report #2

Dear [redacted]

Reference is made to Amendment 030 dated July 22, 1999 which lists the remaining five (5) points to be answered for the Approvable Letter of September 18, 1996. This submission is in response to the point on **Safety Information** noted in Amendment 030 as being outstanding.

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since May 15, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off date for this second report is June 30, 1999. The submission consists of an archival copy and a duplicate clinical review copy.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the French manufacturers, Roussel Uclaf and Exelgyn Laboratories. Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and international product labeling, and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by Exelgyn and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

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

Population Council

The Population Council maintains IND [redacted] on mifepristone and this Safety Update Report #2 includes information that has been previously provided in the IND. We ask that the IND be incorporated by reference in this NDA.

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

Very truly yours,

Sandra Arnold

cc: J [redacted]

SPA: lm

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

ORIG AMENDMENT

The Danco Group

July 14, 1999

[redacted]

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 029 - Responses to FDA Approvable Letter of September 18, 1996

Dear [redacted]

This Amendment 029 provides responses to ten (10) of the nineteen (19) points raised by the FDA in their Approvable Letter dated September 18, 1996. Subsequent filings will respond to the remaining nine (9) points.

For ease of review, this Amendment separately refers to each one of the nineteen (19) points raised and either provides the response, provides a reference to a previous response or indicates that the response will be provided. Responses still to be provided relate to "Drug Product" (4), "Drug Substance" (1), "Safety" (1), "Phase IV Commitments" (1), "Distribution" (1) and "Promotion" (1) and are planned for submission in the near future.

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

Sincerely,

1st

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 [redacted]

ORIGINAL

ORIG AMENDMENT

The Danco Group

July 22, 1999

noted 7/29/99 /S/

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D JUL 23 1999 HFD-580

[redacted]

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 030 - Additional Responses to "FDA Approvable Letter of September 18, 1996"

Dear [redacted]

In our previous Amendment 029 we responded to ten (10) of the nineteen (19) points raised by the FDA in the Approvable Letter dated September 18, 1996. All nineteen (19) points were identified and numbered in that submission.

This Amendment 030 provides responses to the four (4) points relating to "Drug Product"; numbers 5, 6, 15 and 18 (as numbered in our Amendment 029). In addition, we have added to the prior response on one (1) "Drug Substance" point, number 2. This brings our responses to date to fourteen (14) of the total of nineteen (19) points raised in the Letter.

The five (5) responses still to be provided relate to "Drug Substance" (1), "Safety" (1), "Phase IV Commitments" (1), "Distribution" (1) and "Promotion" (1).

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

Sincerely,

/S/

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

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ORIGINAL

The Danco Group

ORIG AMENDMENT
BC

June 30, 1999

[redacted]

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 028 - Chemical, Manufacturing, and Controls (CMC) Section I for Drug Substance: **Supplement**

Dear [redacted]

In connection with our submission of June 3, 1999, we are herewith enclosing, in duplicate, a supplement to the CMC Section submitted as Amendment 025.

This amendment 028 includes the following:

- Annex 1: Mifepristone [redacted] Data
- Annex 2: [redacted] Data

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

Thank you for your attention.

Sincerely,

/S/

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

ORIG AMENDMENT
3C

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

June 25, 1998

Transmitted via Federal Express

[redacted]
Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products
Room 17B-45, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 26 1998
HFD-580

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets
Amendment 015
- **Correspondence regarding recent telephone discussions between [redacted] and**
- **Request for meeting**

Dear [redacted]

[redacted] has informed me that in recent telephone conversations you had discussed the various new manufacturing sites (substance and tableting) that would require pre-approval site inspections. Additionally, you had indicated that Gedeon Richter would also have to be inspected. You had also discussed the fact that the Division had not yet been able to provide the Population Council ~~with a~~ detailed letter of chemistry deficiencies relative to Gedeon Richter's Bulk Drug Manufacturing Information. I would like to add the following comments for the record:

1. While we plan to utilize the existing Roussel Uclaf (RU) bulk drug substance as the primary reference standard, if for any reason the RU reference standard expires or otherwise becomes unstable, we would plan to utilize Gedeon Richter (GR) bulk drug substance as the primary reference standard.

2. Given the above strategy, it is critically important for us to receive a written report of any deficiencies in the September 24, 1997 submission (Amendment No. 9) of the GR CMC as soon as possible. During our March 16 meeting, the Division had identified several deficiencies, and had agreed to try and have a written response to us by the end of May. We understand that there has been some personnel movement but we would still appreciate your earliest possible response to avoid any additional delays. Your assistance in accomplishing this would be appreciated.

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

3. Furthermore, we would like to utilize the already produced GR pilot batches to produce tablets for compassionate use only under an IND, and this would require a review of the September submission of the GR CMC. This material would never be utilized for commercial purposes. As you know, we have no current stock of tablets and compassionate use requests therefore cannot be met, leaving individuals (some with serious diseases) no access to the drug. Since the beginning of 1998, we have received new requests for compassionate use covering meningioma, endometriosis, infertility, uterine fibroids, prostate cancer, cervical ripening, *in-vitro* fertilization, and general research. Of the 19 physicians who received supplies for compassionate use in 1997, 8 have requested additional supplies, and this number may increase as supplies dwindle.

We would also very much appreciate discussions with the Division and Office of Compliance regarding the early scheduling of pre-approval/manufacturing site inspections for the various site locations indicated to avoid time delays. Would it be possible to schedule a meeting during July or early August to discuss the Gedeon Richter CMC deficiencies, the scheduling of the pre-approval/manufacturing site inspections, and the chemistry process utilized by our new manufacturer, including a discussion of the differences from the original process? A representative of our manufacturer will also be available for this requested meeting.

We appreciate your efforts to facilitate the progression of this project. Since I will be away until July 13, 1998 I would recommend that you directly contact ———— , President and Chief Operating Officer of The Danco Group. ————

We would appreciate it if you would please give ———— a copy of this letter. Thank you.

Very truly yours,

Sandra P. Arnold

Sandra P. Arnold
Vice President
Corporate Affairs

APPEARS THIS WAY
ON ORIGINAL

Cc: ————

————

Frederick H. Schmidt, Ph.D.
Patricia C. Vaughan, Esq.

ORIGINAL

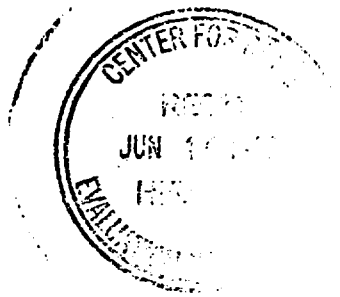
The Danco Group

ORIG AMENDMENT

BC

June 15, 1999

[redacted]



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 026 - Proposed Drug Product Manufacturing Procedure

Dear [redacted]

During a telephone discussion on Friday, June 11 with [redacted] requested Danco to provide the FDA with the manufacturing process that Danco will follow to produce the demonstration and validation batches of Drug Product. We are enclosing this documentation as Amendment 026.

This process is identical to the original Roussel process but, based on our experience during the upcoming production of the demonstration and validation batches, may need minor adjustments which will be reflected in Danco's subsequent Drug Product CMC submission.

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

Sincerely,

/S/

[redacted]

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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Population Council

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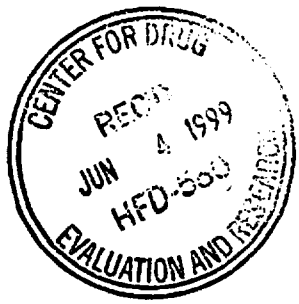
ORIG AMENDMENT

BZ

Sandra P. Arnold
Vice President
Corporate Affairs



June 3, 1999

VIA FEDERAL EXPRESS

[redacted]
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
Amendment 024-Final Reports for the U.S. Clinical Trials on "Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days"

Dear [redacted]

Enclosed are the final reports of the clinical trials entitled "Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days." These trials were conducted concurrently in the United States under identical protocols (166A and 166B) to evaluate the regimen of 600 mg mifepristone followed by an oral dose of 400 μg misoprostol two days later.

The results of these studies are presented in the following series of reports included in this submission:

- Study Report - Efficacy/Safety for Protocol 166A
- Study Report - Efficacy/Safety for Protocol 166B
- Study Report - Acceptability/Feasibility for Protocol 166A
- Study Report - Acceptability/Feasibility for Protocol 166B
- Combined Summary of Effectiveness for Protocols 166A and 166B
- Combined Summary of Safety for Protocols 166A and 166B
- Combined Summary of Acceptability and Feasibility for Protocols 166A and 166B

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

Population Council

Draft versions of the reports for these studies were previously submitted under IND [redacted] Serial Number 185, on May 5, 1997.

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

Very truly yours,

Sandra Arnold

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

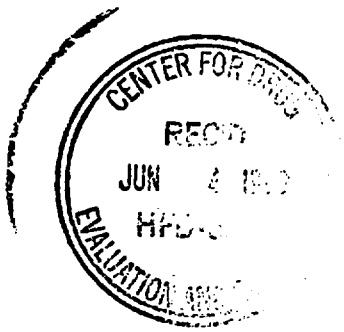
ORIGINAL
ORIG AMENDMENT
BC

The Danco Group

June 3, 1999

[redacted]

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 025- Chemistry, Manufacturing and Controls (CMC) Section for Drug Substance

Dear [redacted]

We are filing the CMC section for our Drug Substance Manufacturer.

We understand that the FDA is under no obligation to review submitted material until the complete response is received. However, as per our discussions with the FDA at the April 9 meeting and reflected in the minutes, we request that the FDA initiate review of this CMC submission as soon as possible.

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

Sincerely,

/S/

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

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ORIGINAL

The Danco Group

ORIG AMENDMENT

May 20, 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, MK 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 023 - Site Details of Drug Product Manufacturer

Dear

We are providing site details for Danco's Drug Product Manufacturer for mifepristone:.

Site and Mailing Address:

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS 151 5/27/99 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

Could you please inform [redacted] as soon as possible that this information has been filed.

Please let me know if you require any additional information.

Sincerely,

/S/

/dns
Enclosure

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

[redacted]

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

ORIG AMENDMENT

The Danco Group

[ ]

BC

May 10, 1999

[redacted]
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 022 — Site Details for Pre-Approval Inspection (PAI) of First Drug Substance Manufacturer

Dear [redacted]

As requested we are providing site details for the scheduling of the PAI for Danco's first Drug Substance manufacturer.

CFN	:	FCCH499
Site Address	:	Shanghai HuaLian Pharmaceutical Co., Ltd. Minle Road, Pudong Development Area Shanghai 201419 People's Republic of China
Mailing Address:		Shanghai HuaLian Pharmaceutical Co., Ltd. 370 Jiang Wan Road (West) Shanghai 200083 People's Republic of China

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 for inspection or copying, or 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 [redacted]

Danco reiterates its statements in Amendment 021: "...this site will be fully ready for inspection in July 1999....Initial communication by the inspector group should be with [redacted] after which [redacted] will be designated Danco's representative."

Please let me know if you require any additional information.

Sincerely,

/s/

/dns
Enclosure

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

APPEARS THIS WAY
ON ORIGINAL

The Danco Group ORIGINAL

April 28, 1999

NDA CORRESP
NC

noted 5/14/99 SJ

[redacted]
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

RECD
APR 29 1999
HFD-580
EVALUATION AND RESEARCH

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 021 – Scheduling of Pre-Approval Inspection (PAI); Submission of Trademark

Dear [redacted]

During the meeting that was held between the Population Council, the Danco Group and the FDA on April 9, 1999, Danco was asked to (i) formally request a PAI for its first Drug Substance Manufacturer in China and (ii) provide alternatives with regard to the trademark for the USAN mifepristone.

Danco hereby requests the FDA to undertake a PAI for Danco's first Drug Substance manufacturing site in China. This site will be fully ready for inspection in July 1999. We understand this coincides with the site inspectors' next visit to the area. Initial communication by the inspector group should be with [redacted], after which [redacted] will be designated Danco's representative.

With regard to the trademark for the USAN mifepristone, Danco's first choice remains MIFEPREX, which was previously submitted on the April 9 agenda document. Danco's second choice is [redacted] Both proposed trademarks have been submitted to the Trademark Office for registration. We understand the concern raised by the FDA about any stem of the USAN being included in the trademark. However, we have researched the Physician's Desk Reference and found numerous examples where USAN stems have been used (see attached). We therefore reaffirm and request positive consideration of MIFEPREX as the prime trademark choice for the USAN mifepristone.

We look forward to receiving the FDA's minutes of the April 9 meeting.

Sincerely,

/S/

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

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

ORIGINAL

NEW CORRESP

The Danco Group

March 31, 1999

[redacted]
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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 0 2 1999
HFD-580

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

- Amendment 020 – Confirmation and Documentation for meeting April 9, 1999 10:00am – 11:30am

Dear [redacted]

This letter confirms our arrangements to attend the April 9, 1999 (10:00am to 11:30am) meeting you have scheduled following our March 30, 1999 telephone call with [redacted] We appreciate the availability of the various Division staff for this meeting.

To facilitate discussion we are enclosing a brief timeline for our Drug Substance and Drug Product manufacturing activities together with targets for submissions to the FDA. (Exhibit 1)

AGENDA

I. Population Council/Danco update on Drug Substance Supply arrangements

A. Status (Exhibit 2)

B. Given the limited visits by the FDA to the country of manufacture, will the FDA be willing to plan ahead and target the Pre-Approval Inspection (PAI) for this site in the June/July period, following an end April/early May Drug Substance CMC submission with three months accelerated stability? (Drug Product CMC with one month accelerated stability will be filed in early June.)

II. Population Council/Danco Update on Drug Substance and Drug Product testing arrangements in the [redacted]

A. Facility

REVIEWS COMPLETED
CSO ACTION:
☐ LE /S/ N.A.I. ☐ MEMO

B. Testing Program

C. Comparisons with original manufacturer's data.

III. Population Council / Danco update on Drug Product Supply arrangements

A. Status

B. Given that Danco is closely following the original manufacturer's procedures and specifications, will the FDA accept an early June Drug Product CMC filing with one month's accelerated stability to start the clock? Danco commits to submitting three and six-month accelerated stability in August and November, as the data become available.

C. Will FDA agree to a PAI of the Drug Product site in July ahead of submission of additional stability data?

IV. Approvable Letter Questions

A. Does the FDA prefer that the Drug Substance / Drug Product questions in the Approvable Letter be responded to at the time of the Drug Substance CMC/ Drug Product submissions or does the FDA prefer one response that covers all questions?

V. Label

A. The label will be resubmitted within the next six weeks

VI. 200mg mifepristone Dosage

A. Status

VII. Trademark
The trademark that Danco is registering for the USAN mifepristone is MIFEPREX

Danco has been diligently preparing its Drug Substance and Drug Product manufacturing sites to produce mifepristone while at the same time being in compliance with both the cGMP requirements of the FDA and the specifications of the original manufacturer. Due to the fact that certain manufacturing aspects of the product had to be restarted post receipt of the Approvable Letter, there are some manufacturing elements that are not completely synchronized from a timing perspective. However, we have made every effort to ensure that any gap in the timing of CMC submissions for Drug Substance and Drug Product is minimized.

The Council/Danco seek the FDA's guidance on how to proceed with various filing and PAI activities in order to minimize any delays in the review and approval process. Specific questions have been included in the agenda.

Planned Attendees: Population Council - Sandra P. Arnold - Vice President Corporate Affairs

Danco -

Sincerely

/S/

CC:

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

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NEW CORRECTED

The Danco Group

BC

Reviewed. This is not a complete response to the 1/27/99 FDA letter. I will review when the sponsor has responded completely to the deficiencies noted in the letter. 1st 3/9/99

February 22, 1999

[redacted]

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 019 – Response to FDA Letter of January 27, 1999
- Correspondence Regarding Teleconference Call of February 10, 1999 with [redacted]

Dear [redacted]

This letter is in response to your letter of January 27, 1999 and the above referenced teleconference, concerning the Population's Council's submissions of August 5 and September 24, 1997. These submissions represent the Gedeon Richter bulk substance manufacturing CMC.

As requested, we are providing our responses to the twelve points raised in the letter. Our responses to points number 2,4,6 and 7 reflect our understanding of the conclusions of our conference call with FDA's chemists on February 10, 1999. If any of these responses indicate a misunderstanding on our part of the FDA's conclusions, please inform us.

[redacted]

We would like to stress that it is our intention to use the Rousssel manufactured bulk mifepristone as the primary reference standard for our new manufacturers' drug substance. If this is not possible, the Gedeon Richter drug substance will be used as the reference standard.

We wish to thank you very much for your letter response concerning the submission of the Gedeon Richter CMC and also appreciate the availability of your chemists for the February 10 teleconference.

Lastly, we request a meeting with the FDA to set dates for the pre-approval inspections of our manufacturing sites and to discuss other issues.

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.I. ☐ MEMO

/S/ 2/10/99

CSO INITIALS

Sincerely,

/S/

CC:

Sandra P. Arnold – Population Council

ORIGINAL
NEW CORRESP

The Danco Group

noted. response to sponsor during 2/10/99 T-con. (S) 2/23/99

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 19 1999
HFD-580

February 8, 1999

[redacted]
Division of Reproductive and
Urologic Drug Products
Room 17B-45, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- **January 27 Letter from** [redacted]

Dear [redacted]

This letter is in response to [redacted] letter of January 27, which commented on the Population Council's submissions of August 5 and September 24, 1997. These submissions represent the Gedeon Richter bulk substance manufacturing CMC.

As discussed on the telephone on Thursday, February 4, we have certain questions concerning the FDA response in the above-mentioned letter. You had suggested that we hold a teleconference with the reviewing chemists and we are providing some of our questions in advance to facilitate discussion.

The questions are:

[redacted]

[redacted]

We look forward to the teleconference at 11:00am on Wednesday, February 10.

Sincerely,

/S/

Cc:
Sandra P. Arnold – Population Council

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A. ☐ MEMO

/S/ 2/6/99
CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CORRESP

151 12/21/98 noted 1/26/99 151

noted 151 12/21/98

December 8, 1998

VIA FEDERAL EXPRESS

[redacted]
Division of Reproductive and
Urologic Drug Products
Room 17B-45, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-687, Mifepristone 200 Mg Oral Tablets
Amendment 018--Correspondence Regarding Changes in Minutes of November 2, 1998 Meeting

Dear [redacted]

Thank you very much for the minutes of the meeting held at your offices on November 2, 1998. I have reviewed them with [redacted], and we respectfully request that you make the following changes:

List of Attendees

- Please correct the spelling of Patricia Vaughan's name to include the second "a", and correct the spelling of "counsel" following her name;
- Please correct the spelling of [redacted] s name to end in "y";
- Please add [redacted]

Discussion Points

- Status Report - Sponsor Presentation

We would appreciate your adding "until an IND supplement is filed" at the end of the next to last bullet.

- September 1997 partial response

We would appreciate it if you could change the first bullet to read: "GR has produced for but not yet transferred to Danco [redacted] of bulk drug substance, pending resolution of manufacturing issues."

- Discussion of Dose Changes - mifepristone and misoprostol

Our recollection is that the fifth bullet should read "A bioavailability study was proposed to demonstrate the equivalence between the vaginal and oral route of administration of misoprostol and these data would be bridged together with effectiveness data."

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Telephone (212) 339-0668 Facsimile (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

We would also appreciate it if you would change the final bullet to read: "the sponsor has not yet made a final decision whether to pursue the use of 600 mg [redacted] of mifepristone."

Decisions Reached
We believe that in the second bullet the term "deficiency letter" should read "approvable letter."

Our recollection of the discussion concerning the review of our partial submission differs in a couple of specifics from your comments in the third bullet. We believe that the Division committed to complete (not *attempt to complete*) the review and produce a report reflecting the outcome of that review by mid December (vs. the end of December).

Action Items
We believe that the "time frame" for the first two action items is mid December, as I have stated above.

Post Meeting Note
The reference to NDA [redacted] should be to NDA 20-687.

Thank you again for arranging for this meeting. We are looking forward to your favorable response to this request for changes to the minutes.

Very truly yours,

Sandra Arnold

cc: [redacted]

Frederick H. Schmidt, Ph.D.
Patricia C. Vaughan, Esq.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE

One Dag Hammarskjold Plaza, New York, New York 10017
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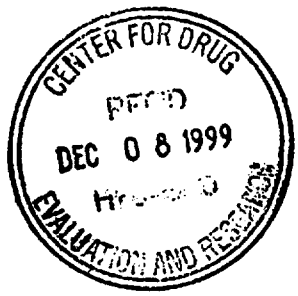
ORIGINAL

The Danco Group

ORIG AMENDMENT
BC

December 7, 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
Amendment 038 - Chemistry, Manufacturing and Controls (CMC) Section 2 for Drug Product: Amendment

Dear

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

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

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

Sincerely,

/S/

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

pulation Council

NC

NEW CORRESP

Sandra P. Arnold
Vice President
Corporate Affairs

no fwd ISI 11/5/98

October 26, 1998

VIA FEDERAL EXPRESS

[redacted]
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

JAT ISI 11/6/98

Subject: **NDA 20-687, Mifepristone 200 mg Oral Tablets**
Amendment 017 - Confirmation and Documentation
for meeting November 2, 1998, 1:00 PM - 2:30 PM

Dear [redacted]

This letter confirms our arrangements to attend the November 2, 1998 (1:00 PM - 2:30 PM) meeting you have scheduled in response to our June 25, 1998 letter. We appreciate the availability of the Division staff for this meeting.

The broad agenda items were presented in the June 25 letter and are detailed below:

FINAL AGENDA

I. Population Council/Danco update on Drug Substance supply and Drug Product tableting arrangements:

A. Status

II. Review of the FDA's assessment of the CMC from Gedeon Richter (GR) (submitted September 1997) and use of the GR produced pilot batches as standards, initially discussed at our meeting in March:

A. What deficiencies have been noted on the written review of the CMC by the FDA reviewers?
B. When will the letter detailing the deficiencies in the Gedeon Richter CMC be provided?

III. Discussion by [redacted] Drug Substance manufacturers, of the process used to produce mifepristone in laboratory scale and subsequently to be used for validation and commercial batch production:

A. Is the FDA comfortable with the process approach being taken?
B. Will using this process, which is almost identical (*e.g.*, the same) to Roussel-Uclaf's ("RU" 's) Process obviate any equivalence requirements?

IV. [redacted]

V. Discussion of the FDA pre-approval inspection of the bulk Drug Substance manufacturers:

A. Can the FDA confirm that it could be willing to undertake early Drug Substance manufacturer site inspections, ahead of complete filing?

VI. Discussion of commercial sources producing [redacted] and the manufacturer's plan to test and characterize this starting raw material

VII. Timing of CMC submissions for bulk Drug Substance and Drug Product tablet production

As previously advised, while we plan to utilize the existing RU bulk Drug Substance as the primary reference standard, if for any reason the RU reference standard expires or otherwise becomes unstable, we would plan to utilize GR bulk Drug Substance as the primary reference standard. This is why we are so interested in the FDA's report and comments on the CMC from GR.

In our efforts to produce mifepristone in [redacted] bulk Drug Substance manufacturing sites, we have endeavored to follow the RU process as closely as possible with only very minor modifications. The representative from one of our manufacturers will describe the process so that the FDA can be informed of the approach we are taking. Based on previous comments by the FDA, and given the process as described, we do not expect to be required to undertake any equivalence testing.

During our March meeting, we raised the issue of the potential for physicians to use [redacted] instead of 600 mg mifepristone. We believe that we have to address this issue head-on and in a timely manner so that we are not faced with [redacted] mifepristone tablets and using the tablets for [redacted]

Very truly yours,

for Andrea Arnold

cc:

Frederick H. Schmidt, Ph. D.
Patricia C. Vaughan, Esq.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

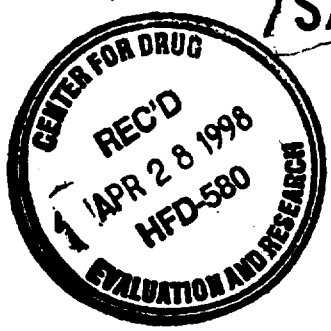
Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CORRESP

noted 5/4/98 /S/

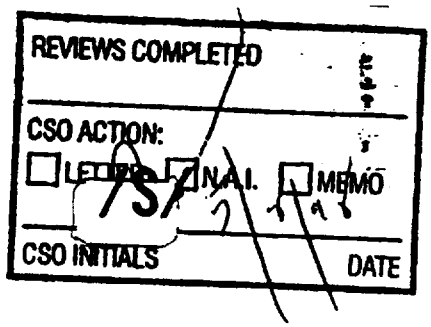
/S/ 5/8/98



April 27, 1998

Transmitted via Federal Express

[redacted]
Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products
Room 17B-45, HFD-580
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 014—Correspondence regarding Minutes of March 16, 1998 meeting

Dear [redacted]

Thank you very much for providing us with a copy of your minutes for our March 16, 1998 meeting about Chemistry, Manufacturing, and Controls (CMC) issues. We have reviewed the minutes and are in agreement that, for the most part, they accurately reflect the general conversation and decisions reached. However, there are a few small, but important, points that we request be clarified in the official minutes.

Although [redacted] was listed as a planned attendee, he was unable to be present at the meeting. Therefore, his name should be deleted from the list of attendees. Likewise, we believe that an FDA representative, [redacted] was not in attendance and should be deleted from the list of attendees. Additionally [redacted] Ph.D., Vice-President, Manufacturing" and Patricia Vaughan's name was misspelled and should be corrected to "Patricia C. Vaughan, Esq.—Legal Counsel."

During our discussion relating to reference standards, we explained that our plan is to utilize existing Roussel Uclaf (RU) bulk drug substance as a reference standard, but that in the event that the RU reference standard expires or otherwise becomes unstable, we plan to utilize Gedeon Richter (GR) bulk drug substance as the reference standard. As currently written, the minutes suggest that we plan to utilize the GR bulk drug substance as the primary reference standard. We would appreciate your revising the minutes to reflect that GR will be used only as a back-up

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reference standard and the existing RU bulk drug substance will be utilized as the primary reference standard.

Finally, during the meeting we discussed the possibility of a tableting site change prior to approval of the NDA. [redacted] suggested that it would be appropriate to follow the Agency's SUPAC-IR guidance document if a tableting site-change occurred prior to approval of the NDA. We would appreciate this suggestion being incorporated in the official meeting minutes.

Thank you for your assistance in this matter. Please contact me should there be any questions or comments regarding our request.

Very truly yours,

Sandra Arnold

cc: [redacted]

Frederick Schmidt, Ph.D.
Patricia C. Vaughan, Esq.

APPEARS THIS WAY
ON ORIGINAL

Telephone: (212) 339-0500 Facsimile: (212) 755-6052 One Dag Hammarskjold Plaza, New York, New York 10017
Email: pubinfo@popcouncil.org http://www.popcouncil.org

Population Council

noted 2/24/98

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CORRESP

February 19, 1998

VIA FEDERAL EXPRESS

[redacted]

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RE: NDA 20-687, MIFEPRISTONE 200 MG ORAL TABLETS
AMENDMENT 013 - CONFIRMATION AND DOCUMENTATION
FOR MEETING MARCH 16, 1998 - 2:00 p.m.-3:30 p.m.

Dear [redacted]

This letter confirms our arrangements to attend the March 16, 1998 (2:00 p.m. - 3:30 p.m.) meeting you have scheduled in response to our January 30, 1998 letter. We appreciate your timely response and the availability of the Division staff for this meeting.

The Agenda for the meeting was presented in the January 30 letter and remains current as restated below:

FINAL AGENDA

I. Plan for amending NDA to include new bulk drug substance manufacturer:
   - A. Discussion of FDA's assessment of the CMC from Gedeon Richter and use of their pilot batches as standards,
   - B. Discussion of demonstrating comparability to Gedeon Richter bulk drug substance given the perceived differences from the Roussel process,
   - C. Discussion of demonstrating comparability of the new bulk drug substance to the Roussel material.

II. Discussion of the possible use of Gedeon Richter pilot batches for compassionate patient use in the United States.

III. [redacted]

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

As you may remember, at our meeting on August 11, 1997 we sought your concurrence to use the pilot batches of Gedeon Richter bulk drug substance as a "gold standard," to validate a future manufacturer(s), particularly as no drug substance was available from Roussel. The information on manufacturing provided by Gedeon Richter was submitted for your review in prior amendments in 1997.

During that meeting, we discussed efforts to secure bulk drug substance from Roussel. The Population Council has a small quantity of bulk drug substance from Roussel which is within its original dating period. This material expires in 1999 and although it is very stable, we have no assurance that it will continue to remain stable; therefore, starting at the expiration date, we plan to continually revalidate this material. Thus, we need to know whether FDA would allow us to use the Gedeon Richter bulk drug substance as a "gold standard," if the Roussel material loses stability.

We are enclosing an analysis of the discrepancies our experts have found between the Roussel process and the Gedeon Richter process (Attachment A), as a basis for discussion of the utility of the Gedeon Richter bulk drug substance. During our meeting (Agenda Item IB), we would like to discuss the nature of these differences and what effect they may have on your allowing us to use the Gedeon Richter bulk drug substance as a "gold standard" in validating new manufacturing operations. We need to know, preferably in writing, the potential utility of the Gedeon Richter material, based on the manufacturing information obtained from Gedeon Richter and filed in Amendments No. 8 (August 5, 1997) and 9 (September 24, 1997). If additional data are needed to support use of the Gedeon Richter bulk drug substance as a "gold standard," then would the Agency be specific as to what data are needed to allow such use?

The enclosed material (Attachment A) is being provided in advance for your review. Additionally, we will make a short presentation to update you on our new manufacturer and timelines, and then wish to proceed with an open discussion of the agenda items. Please call me if you have any questions or need additional materials before the March 16th meeting.

Very truly yours,

Sandra Arnold

Attending the March 16th Meeting:

Sandra Arnold, Population Council

Patricia C. Vaughan, Esq. Population Council
Frederick Schmidt, Ph.D., Population Council

APPEARS THIS WAY
ON ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

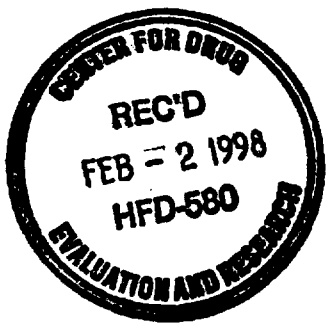
ORIGINAL

NEW CORRESP

/S/ 2/27/98

noted 2/6/98 /S/

noted /S/ 2-25-

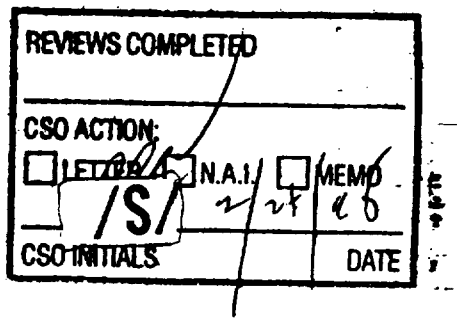


January 30, 1998

VIA FEDERAL EXPRESS

[redacted]

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 012-Authorization for NeoGen to Interact with FDA on NDA

Dear [redacted]

This amendment number 012 to NDA 20-687 authorizes the FDA to communicate directly with certain representatives of NeoGen investors, L.P. (NeoGen) in all matters relating to our pending NDA 20-687 (mifepristone 20 mg Oral Tablets). NeoGen is the U.S. Licensee of The Population Council for mifepristone and will be commercializing mifepristone when the NDA is approved. We believe that direct communication between NeoGen and the FDA about our pending NDA will facilitate the regulatory process. The ability of NeoGen to communicate with you is an addition to the existing communication channels between The Population Council and the FDA. Let me reassure you that NeoGen communications with the FDA will be discussed in advance with The Population Council to prevent duplication or differences.

The Population Council will continue at this time to retain the ownership of the NDA, and will be in communication with NeoGen regarding any direct discussions with the FDA. Therefore, official written notices should continue to be directed to our attention at The Population Council.

You are hereby authorized to communicate directly with the regulatory attorney for NeoGen, [redacted] is an attorney experienced in FDA statutes and regulations and was [redacted]. In addition, you are hereby authorized to communicate directly with [redacted] who is President and Chief Operating Officer of The NeoGen Group, [redacted] Mr.

One Dag Hammarskjold Plaza, New York, New York 10017
http://www.popcouncil.org

[redacted] in Marketing and Business Development.

If you have any questions about this authorization, please don't hesitate to contact me to discuss them.

Very truly yours,

Sandra P. Arnold
Vice President, Corporate Affairs
The Population Council

cc: [redacted]

APPEARS THIS WAY
ON ORIGINAL

Population Council

This is not the complete response received 10/2/97 IST

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

ORIG AMENDMENT
BC

REVIEWS COMPLETED		
CSO ACTION:		
☐ LETTER	☐ N.A.I.	☐ MEMO
IST	1/27/99	
CSO INITIALS		DATE

September 24, 1997.

[redacted]
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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 2 9 1997
HFD-580

RE: NDA 20-687, Mifepristone 200 mg Oral Tablets
Amendment 009 - Chemistry, Manufacturing and Controls

Dear [redacted]

During your August 11, 1997 meeting with the Population Council and our licensee, we mentioned that we anticipated receiving additional CMC information from Gedeon Richter in September, and that we would provide that information to you promptly. The willingness you expressed during that meeting to review this revised CMC material and to provide written questions within the next month or so as to any additional information necessary is appreciated. Any questions you might have should be directed to my attention and we will forward them to Gedeon Richter to obtain additional information as expeditiously as possible. We are anxious to obtain the Division's feedback as to whether the current pilot batches can be used as standards to bring on new production facilities at another site.

We are supplying in this Amendment 009 an amended CMC section to our NDA number 20-687. Amendment 009 includes all the new information we recently received from Gedeon Richter, integrated into our August 5, 1997 amendment. Please be advised that our August 5, 1997 Amendment was incorrectly numbered "006" when it should have been "008" and also there were a few pages which were misnumbered or missing page numbers. These errors have been corrected in the enclosed Amendment 009.

This amended CMC differs from our August 5, 1997 amendment in the following ways:

- The following pages in this Amendment 009 are new: 6.1, 6.2, 62.1, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, and 151.7.

- The following pages in this Amendment 009 replace the same pages in the August 5th submission: 8, 9, 10, 12, 22, 23, 39, 41, 42, 53, 55, 56, 60, 62, 93, and 139.

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

To facilitate your identification of the new materials and your quick review, we have tabbed the new and replacement pages. We look forward to hearing from you as soon as you have had an opportunity to evaluate these materials.

Very truly yours,

Sandra Arnold

Enclosure

cc:
Advances/The NeoGen Group

Dr. Ann Robbins
The Population Council

Dr. Frederick Schmidt
The Population Council

APPEARS THIS WAY
ON ORIGINAL

N 20-687

Population Council ORIGINAL

Mailed 8/11/97 ZSL

Margaret Catley-Carlson
President

NEW CORRESP

August 5, 1997

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
/S/ 11/27/99
CSO INITIALS DATE

FDA, Division of Reproductive & Urologic Drug Products
5600 Fisher's Lane
Rockville, MD

Dear

Thank you very much for arranging for our meeting on August 11 on very short notice. We recognize the difficulty of assembling the appropriate FDA staff for the meeting, particularly during the summer vacation season, and appreciate your efforts.

The meeting materials enclosed are:

- Our proposed agenda, including a list of the participants from the Population Council and our licensee for mifepristone, Danco Laboratories/The NeoGen Group.
- Our regulatory proposal on the pending NDA.
- The questions we would like to have answered by the FDA.

In addition, we are supplying an amended CMC Section to our NDA number 20-687, dated March 14, 1996. The arrangement that has been worked out with Gedeon Richter is that the Population Council will file Gedeon Richter's Drug Master File information as part of the Council's CMC Section. The enclosed amendment contains the manufacturing information and data that Gedeon Richter has thus far supplied to the Population Council. Also included in the amendment is a list of the additional information Gedeon Richter will provide on September 9, 1997.

As you requested, we have prepared some questions to help focus the discussions at the meeting. The Population Council and Danco Laboratories look forward to our meeting, where we hope to review our plan to obtain approval of the pending NDA on the basis of the Gedeon Richter information, and the substitution of a new bulk drug manufacturer post approval.

With very best wishes,

Margaret Catley-Carlson

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 06 1997
HFD-580

Telex

One Dag Hammarskjold Plaza, New York, New York 10017

N 20-677

NEW CORRESP

ORIGINAL

Population Council

Charlotte Ellertson
Program Associate
Phone: (212) 339-0607
Email: cellertson@popcouncil.org

faxed 8/18/97 /S/

to mifepristone NDA clerk

/S/ 8/20/97

noted /S/ 8-18-97

REVIEWS COMPLETED

CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO

/S/ 8/22/97 ap

CSO INITIALS DATE

July 28, 1997

[redacted]
Food and Drug Administration
Park Lawn Building, HFD-510
5600 Fishers Lane
Rockville, MD 20857

Dear [redacted]

Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result of this approach to handling the data is that certain aspects of our future publications may differ from tabulations that appear in our regulatory submissions.

If this letter reflects your understanding of our conversation also, would you please sign below and return the letter to us?

Thank you again for your assistance.

Sincerely,

Sandy Writing for Charlotte Ellertson

Charlotte Ellertson
Program Associate

CENTER FOR DRUG REC'D AUG 14 1997 HFD-580 EVALUATION AND RESEARCH

This letter accurately represents our telephone conversation.

/S/ [redacted]

8-12-97
Date

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0500 Facsimile: (212) 755-6052 Email: pubinfo@popcouncil.org http://www.popcouncil.org

ORIGINAL

The Population Council
Center for
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1230 York Avenue
New York, New York 10021
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Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

VIA Fed Ex

March 31, 1997

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS /S/ DATE 1/27/98

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

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets
Amendment 007 - Information Requested on Physician Labeling
in the Approvable Letter

Dear [redacted]

In response to the NDA approvable letter dated 18 September 1996, we are submitting revised Physician Labeling for NDA 20-687. Appendix I contains a letter prepared by Dr. Charlotte Ellertson of the Population Council, providing a detailed description of, and rationale for, our responses to requests from the FDA in the NDA approvable letter. Appendix II contains a copy of the revised labeling and Appendix III contains a marked version of the labeling which indicates the changes made from the version submitted in our NDA application on March 14, 1996. As discussed in a telephone conversation with [redacted] last week, an annotated version of the revised labeling is not being submitted at this time. However, we will provide a new annotated version of the labeling once it is finalized, if requested by the FDA.

We would like to request a meeting with the FDA to discuss this revised labeling. We propose the meeting take place in late April and includes 5-7 people from the Population Council staff. I will contact [redacted] with specific dates, attendees and agenda.

Thank you for considering the revised labeling. We look forward to working with the FDA to finalize this document.

Sincerely

Ann Robbins

Ann Robbins, Ph.D.
Scientist

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 0 1 1997
HFD-580

The Population Council
er for
medical Research

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New York, New York 10021
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noted 2/5/97 /S/

ORIGINAL

/S/ 2/7/97

noted /S/ 2-5-97

VIA Federal Express

January 30, 1997

NEW CORRESP

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 31 1997
HFD-580

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

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets
Amendment 006 - Information Requested on
Drug Substance in the Approvable Letter

Dear [redacted]

As discussed in a telephone conversation with [redacted] Consumer Safety Officer, on January 28, 1997, the Population Council can now begin to respond to the requests for information raised in the September 18, 1996 approvable letter for mifepristone NDA 20-687. Our plan is to supply the FDA with the requested information for specific topics as the issues are resolved and/or the information becomes available. In this letter, we are proposing our strategy for responding to the FDA's request for additional information on several aspects of the drug substance.

The Population Council has identified a new manufacturer of the drug substance. Our new manufacturer can provide answers to all of the specific questions and requests in the approvable letter, including the description of the synthesis from an appropriate starting material, which is prior to [redacted] in the synthetic pathway. This starting material has been identified and accepted in DMFs submitted to the FDA by other companies. Our expectation is that this is the same starting material used by the manufacturer currently identified in our NDA. Our new manufacturer is prepared to submit a DMF for mifepristone synthesis from this starting material to the FDA and provide information to respond to all inquiries in the approvable letter.

I respectfully request a response in writing from you and/or your colleagues in the division on the acceptability of the Council's strategy to respond to the drug substance issues with information provided by our new manufacturer rather than the manufacturer currently identified in the NDA. Once this approval is obtained, our new manufacturer will proceed with the filing of the DMF and the Council will proceed with the submission of the information on the drug substance requested in the NDA approvable letter. If the FDA requires additional details, the Council and our new manufacturer can discuss this with the division at a meeting or in a conference call.

In accordance with 314.60 (c), we certify that a copy of this amendment has been sent to our FDA district office.
Thank you for your attention to this matter and I look forward to your response.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yaho

cc: Food and Drug Administration

[redacted]

APPEARS THIS WAY
ON ORIGINAL

The Population Council

er for
Medical Research

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

Noted 10/1/96 /S/

/S/ 10-1-96

ORIGINAL

/S/ 10/3/96

September 26, 1996

5NC

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

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.L. /S/ 9/26/96
CSO INITIALS DATE

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets
Amendment 005 - Response to Approvable Letter

Dear [redacted]

Reference is made to our above New Drug Application for mifepristone which was received by your office on March 18, 1996. We also refer to the correspondence of September 18, 1996, signed by [redacted] informing us that the application is approvable.

We appreciate your prompt review of our application and, in accord with 21 CFR 314.110, wish to inform you of our intent to file an amendment to the application to address the matters discussed in the approvable letter. That amendment will be submitted promptly upon the availability of appropriate information to respond to the requests of the agency.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yho

REC'D
SEP 30 1996
HFD-580 ARCH

The Population Council

enter for
iomedical Research

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VIA FEDEX

September 16, 1996

APPEARS THIS WAY
ON ORIGINAL

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

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

Dear [redacted]

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

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

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

The Population Council

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

Sincerely,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yho

APPEARS THIS WAY
ON ORIGINAL

Population Council
er for
edical Research

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NEW CORRESP

VIA FEDEX

August 15, 1996

APPEARS THIS WAY
ON ORIGINAL

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

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets/Amendment 003

Dear [redacted]

We refer to our above New Drug Application for mifepristone which was submitted on March 14, 1996. As discussed in telephone conversations with [redacted] we wish to amend our application with the following information:

Appendix I contains the Certification Statement for the Generic Drug Enforcement Act of 1992, which should have been included in our NDA Submission. I apologize for this omission. Appendix II contains a description of the proposed U.S. distribution system for the use of mifepristone and misoprostol for termination of early pregnancy.

Please contact me if you have any questions or need further information.

Best regards.

Ann Robbins, Ph.D.
Scientist

AR/yho

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 19 1996
HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 16 1996
HFD-510

The Population Council
Center for
Biomedical Research

ORIGINAL

1230 York Avenue
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Telephone: (212) 327-8748
Facsimile: (212) 327-7678
E-mail: robbins@popcbr.rockefeller.edu

July 25, 1996

ORIG AMENDMENT

N-511

Via FedEx

[redacted]
Division of Reproductive and
Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear [redacted]

This is a follow-up to your telephone call yesterday, July 24, 1996, requesting a summary of the international post-marketing surveillance data on the use of mifepristone. Enclosed please find a copy of the relevant sections of the Population Council NDA 20-687 and NDA Safety Update. I've indicated where each of these pieces of information is located within the NDA or NDA Safety Update.

These summaries represent all the safety information available to us from Roussel Uclaf's international (France, Sweden, United Kingdom) post-marketing surveillance reports, starting from 1989, the first year mifepristone was on the market in France. You will note that the International Safety Reports begin in January 1, 1991. Prior to this time, a written summary report was not available from Roussel. However, the individual adverse events that occurred starting from 1989 were given to us by Roussel on a diskette database and are included in the listing in Table 7 of the NDA sections attached here. I am currently trying to determine if at this time Roussel has a more comprehensive, all-inclusive document covering this information, rather than the three separate, but chronologically consecutive International Safety Reports and the information extracted from the diskette database. This was not available from them at the time of our NDA submission. Meanwhile, I am also attempting to contact the relevant people in Sweden and the United Kingdom to determine if there are separate post-marketing surveillance reports for each of these countries.

Yesterday during our telephone conversation, [redacted] requested that she see a summary of this information in the NDA and asked that I send it via you. Would you please forward a copy of all of the information in this FedEx package to her? Thank you very much.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

I will be on vacation from July 29 - August 5. I will call you on August 6 to obtain feedback from the division on this issue as well as to relay any additional information I may have by then.

Sincerely yours,

Ann Robbins, Ph.D.
Scientist

cc: [redacted] letter only, via fax: [redacted]

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

The Population Council

Center for
Biomedical Research

1230 York Avenue
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June 20, 1996

[redacted]
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets
Safety Update Report

Dear [redacted]

Reference is made to our above New Drug Application for mifepristone which was submitted on March 14, 1996. We also refer to your correspondence of May 7, 1996 informing us that the review priority classification for the application has been changed to a priority (P) review.

We have been advised that as a result of the change in classification, the timing of the submission of the Safety Update Report should be advanced and we are therefore forwarding the enclosed report at this time.

This update report has a cut-off date of May 15, 1996 and includes new information received since the cut-off date of August 1, 1995 for the original submission of the application. Included in this report are four new nonclinical and two new clinical study reports as well as new information regarding study reports previously submitted in our application. All new study reports have been previously submitted to IND [redacted] and the locations of those submissions in the IND are stated on the Index to this update report.

This submission includes an archival copy as well as a technical review copy for the nonclinical pharmacology and toxicology information and a technical review copy for the clinical information. The archival and each technical review copy contain a copy of this cover letter, the new drug application form (Form FDA 356h), the introduction and the index to the complete update report. In addition, appended at the end of each technical review copy is a copy of the summary information from the other technical

review copy. This summary information retains the page numbers of the individual volume from which it was removed.

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

Sincerely yours,

Ann Robbins

Ann Robbins, PhD
Scientist

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Population Council
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

Fax from Ann Robbins
Phone: 212-327-8748
Fax: 212-327-7678

Number of Pages (including this sheet): 2

Send to Facsimile Number: 9-1-301-443-0072

Date: 7 May 1996

Send to Company: FDA; Div. Metabolic & Endocrine Drug Products

Send to Person: [redacted]

Subject: Request for meeting

Dear [redacted]

I would like to request a meeting with the division to discuss a variety of issues regarding NDA 20-687 and activities associated with the mifepristone project. Although this can be considered a request for a "90 day meeting" to discuss the review of the NDA, as you can see from the suggested agenda items (attached), there are several other issues we would like to discuss at this meeting. Dates that are possible for Council staff to visit the FDA are May 23, 28 (before 3pm), 29-31, June 3 - 7.

Please let me know at your earliest convenience if this meeting can be arranged. Thank you in advance.

Best regards,

Ann Robbins, Ph.D.
Scientist

APPEARS THIS WAY
ON ORIGINAL

SUGGESTED AGENDA

1. Change of review status from "S" to "P"

2. Safety Update
   - timing
   - content

3. CMC
   - starting material
   - FDA inspection of manufacturer
   - status of new manufacturer of active ingredient and dosage form

4. Advisory Committee Meeting

5. FDA Audit of the French Clinics

6. Data from the U.S. Trials

APPEARS THIS WAY
ON ORIGINAL

ne Population Council
nter for
dical Research

1230 York Avenue
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Telephone: (212) 327-8731
Telex: 238274 POBI UR

April 19, 1996

[redacted]
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-687 - Mifepristone 200 mg Oral Tablets/Amendment 001

Dear [redacted]:

We refer to our above New Drug Application for mifepristone which was submitted on March 14, 1996. With this amendment to the application, we wish to provide additional information for the samples, methods validation and labeling section and the clinical section of the application as follows:

NDA Item 4 - Samples, Methods Validation and Labeling

As noted in Appendix I (Volume 2/Page 156) of the methods validation information in the original submission of the application, a tabular listing of all samples to be submitted was not available at the time of the original submission. This information has now been received from the product manufacturer and is included as **Attachment I.**

NDA Item 8 - Clinical Data Section

~~As noted~~ on the title page (Volume 87/Page 289) of the clinical expert report entitled *"Rapport d'Expert Clinique - Expulsion du Contenu Utérin dans la Mort Foetale in Utero"* in the original submission, the report was available only in French at the time of the submission. An English translation of the report has ~~now been~~ obtained and is included as **Attachment II.**

This submission includes an archival copy containing all information described above. In addition, included are three technical review copies of the amendment to the methods validation information and one technical review copy of the amendment to the clinical section. Each archival and technical review copy includes a copy of the cover letter, new drug application form (Form FDA 356h) and index to the amendment.

[redacted]
Food and Drug Administration
April 19, 1996

Please contact me should there be any questions or comments regarding the above information.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

Attachments: Described above.

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Medical Research

1230 York Avenue
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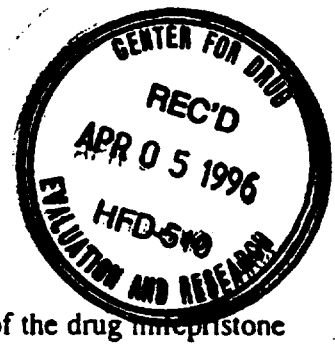
March 14, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857



Subject: NDA 20-687 **Mifepristone Tablets, 200mg**

Dear Madam/Sir:

We submit herewith a New Drug Application to provide for use of the drug mifepristone in the induction of abortion.

The application has been compiled in accordance with appropriate guidelines issued by the Food and Drug Administration. In addition, the submission includes in Volume 1.1 a section entitled "Introduction to the New Drug Application." This section contains a brief overview of the development history of the product and of major contacts with the agency regarding the application. The section also includes a description of the general procedures followed in assembling the application and provides information on the contents of each section of the application.

As described in the application and discussed previously with the reviewing division, to preserve confidentiality, information for Item 3 (Chemistry, Manufacturing and Controls) of this application has been submitted separately by the manufacturer to IND [redacted] (Submission No. 135) on behalf of the Population Council. The methods validation portion of Item 4 (Information on Samples, Methods Validation, and Labeling) was compiled by the manufacturer and provided to the Population Council for inclusion in this application.

A check for $102,000.00, which is 50% of the application fee, has been sent via Federal Express to the Food and Drug Administration at the lockbox address of Mellon Bank, Pittsburgh, PA. User Fee I.D. #2972 has been assigned to the Mifepristone NDA. User Fee Form #3397 is appended to this letter.

If there are any questions regarding this application, please contact the undersigned at (212) 327-8748.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

Attachment: User fee coversheet form 3397
NDA 20-687

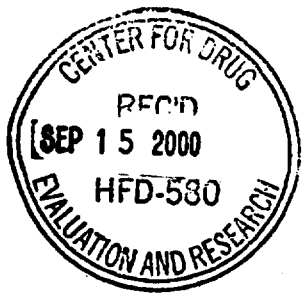
ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 15, 2000

BL
ORIG AMENDMENT



[redacted]
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 060; Further response regarding
open issues

Dear [redacted]

I am enclosing the prescribing information (package insert), Prescriber's Agreement, Order Form, Medication Guide, and Patient Agreement, as revised in accordance with discussions this week.

Also, although we do not believe that the application of 21 CFR Sections 314.500-560 is appropriate, we agree to its application as part of the approval of this NDA.

We commit to conduct post-approval the following studies:

I. A cohort-based study on safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills as compared to physicians who refer their patients for surgical intervention. Previous study questions about age, smoking, follow up on day 14 (compliance with return), as well as an audit of signed Patient Agreement forms, will be incorporated into this study.

II. A surveillance study on outcomes of ongoing pregnancies

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Sandra P. Arnold 9/15

Sandra P. Arnold

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Teleconference Meeting Minutes

Date: September 14, 2000 **Time:** 1:00 – 2:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair:

Minutes Preparer:

FDA Attendees:

, Office of Evaluation III (ODEIII; HFD-103)
, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
, DRUDP (HFD-580)
, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
, Division of Drug Review and Evaluation II (DDREII; HFD-440)
, DDREII (HFD-440)
, DDREII (HFD-440)
, DDREII (HFD-440)
, Project Management Staff, DRUDP (HFD-580)
, Regulatory Project Manager, DRUDP (HFD-580)

External Lead: Nancy Buc

Meeting Objective: To discuss the Information Request Letters sent September 13 and 14, 2000.

Discussion:

Labeling

- the Agency accepts the manner in which the sponsor is using the trademark symbol and the capitalization of the name "Mifeprex"
  - all CAPS and ™ when used for the first time in any document
  - the second appearance the first letter capitalized with the trademark and an asterisk indicating the trademark belongs to Danco
  - anytime after that it will be first letter capitalized with the asterick
- the sponsor is reviewing the addition of the phrase "with a terminal half-life of 18 hours" and the addition of acid in the first sentence in the Distribution section of the label
- the sponsor agrees to the removal of the section on in the **WARNINGS** section of the label

- in the **PRECAUTIONS** section of the label, the sponsor will respond to the elimination of the phrase [redacted] and replaced with "qualified physician"
- in the **PRECAUTIONS** section, Information for the Patient subsection [redacted] has been deleted
- replaced [redacted] with Medication Guide wherever it is used throughout the label
- in the **PRECAUTIONS** section, Drug Interaction subsection, the sponsor agrees with the deletion of the first paragraph and the replacement wording provided for by the biopharmaceutics reviewer
- in the **PRECAUTION** section, Carcinogenesis, Mutagenesis, Impairment of Fertility subsection, the sponsor agrees to the change of the word [redacted] to genotoxic and also the elimination of sentence [redacted]
- in the **PRECAUTIONS** section, Teratogenic Effects subsection, heading Human Data, the sponsor will provide the Agency with the correct numbers of patients since May 2000, and agrees with the number changes the Agency made
- the sponsor agrees with the changes made to Table 2 to update the numbers
- in the **OVERDOSAGE** section the sponsor will provide the Agency with a reponses to changing the [redacted] to "acute lethal dose"
- in the **DOSAGE AND ADMINSTRATION** section the sponsor will change the last sentence to match bullet number 3 of the **PHYSICIAN AGREEMENT**
- in the **DOSAGE AND ADMINSTRATION** section, Day One: Mifeprex Administration subsection should read as follows: "Patient must read the Medication Guide and read and sign the PATIENT AGREEMENT"
- in the **DOSAGE AND ADMINSTRATION** section, Day 3 : Misoprostol Administration subsection, the sponsor agrees to the suggested changes in both paragraphs
- in the **DOSAGE AND ADMINSTRATION** section, Day 14: Post-Treatment Examination subsection, the sponsor agrees with the proposed changes
- in the **HOW SUPPLIED** section the sponsor agrees with the proposed changes

PATIENT AGREEMENT

- the sponsor was not prepared to discuss the changes faxed to them in the September 14, 2000 Information Request letter

ORDER FORM

- the sponsor agrees to the addition of a date line for the date of signature

PRESCRIBER AGREEMENT

- the sponsor agrees with the addition of the numeric digits following the "1-877-4 Early Option" phone number
- the sponsor agrees with the change of [redacted] to "administration" in the last paragraph
- the sponsor will add the distributors name, address, phone number, fax number, and website to the end of this document

Phase 4 Commitments

- the sponsor needed clarification of the term "Emergency intervention"; the Agency defined it as medically necessary intervention (i.e. heavy bleeding)
- the sponsor will need to respond with the commitment to perform the Phase 4 studies in a submission to the NDA
- the sponsor has reservations regarding educating the patient about reporting an ongoing pregnancy after the medical abortion fails; the Agency would like the sponsor to consider some type of method

for the patient to report an ongoing pregnancy in event that the physician does not report the pregnancy

- the sponsor will need to address adding the language from the most recent European label as a contraindication for inherited porphyria in the label

Action Items:

- the sponsor must to submit the revised label, agreement to Subpart H, and the commitment to perform studies
- meeting scheduled for September 15, 2000 at 11:00 AM to discuss the remaining issues
- fax meeting minutes to the sponsor within 30 days

/S/
Minutes Prepared

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 25, 2000 **Time:** 3:30 – 4:00 PM **Location:** Parklawn; 17B-43

NDA 20-687 **Drug:** Mifepristone 200 mg Tablets

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance (statistics)

Meeting Chair: [redacted]

Meeting Recorder: [redacted]

External Lead: Nancy Buc

FDA Attendees:

[redacted], Office of Drug Evaluation III (ODEIII; HFD-103)
[redacted], Division of Reproductive and Urologic Drug Products (DRUDP ; HFD-580)
[redacted], Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
[redacted], Project Management Staff, DRUDP (HFD-580)

External Attendees:
Beverly Winikofi, M.D. – Population Council
Shelley Clark, Ph.D. – Population Council
Heather O'Neill – Danco Laboratories, LLC
Nancy Buc – Buc & Beardsley

Meeting Objective: The applicant requested this teleconference to clarify FDA-derived sample size calculations and to confirm the study endpoints for the referring versus non-referring physician study for post-approval (Phase 4 commitment) protocol.

Background: In teleconferences before August 23, 2000, FDA conveyed suggestions for study designs, endpoints and sample size estimates. The applicant's interpretation of the sample size calculations and endpoints are contained in their August 23 letter.

Discussion Items:

- Success rates of 92% and 95% were demonstrated in the clinical trials; rates of transfusions and hospitalizations were less than 1%
- the applicant is concerned the sample size of 120 per group is inadequate to yield a satisfactory upper limit of a confidence interval for the rate of a serious adverse event, such as transfusion, if the rate of a serious adverse event is approximately 1%

- endpoints of interest to be compared between the two groups need to include the success rate.(e.g., approximately 92 or 95%) and its converse, the failure rate (i.e., 1- success rate); most failures, if not all, will likely result in surgical termination of pregnancy
- other endpoints of interest include rates of complication, (such as transfusions, hospitalizations, etc.)
- FDA would like to exclude an absolute difference of greater than 5% in efficacy between the two groups
- FDA also would like to exclude an absolute difference of greater than 5% in complication rates between the two groups
- FDA requests complication rates estimated separately for each group, but these estimates are not the ultimate goal of the Agency
- DRUDP agreed with the applicant's concern that 120 patients per arm is inadequate to yield an acceptable upper limit of a confidence interval for an estimated complication rate *within* a group; however, 120 patients is adequate for ruling out differences in rates of greater than 5% *between* groups.
- The FDA-derived estimate of 120 patients per arm was based on the following assumptions:
  - the endpoint is rate of complications
  - the referral and non-referral groups each have an underlying rate of 1%
  - the rates for the two groups do not differ by more than 5%
  - a 95% one-sided confidence interval for the differences in rates
  - approximately 80% power
  - a randomized study
  - no adjustments for dropouts
- DRUDP indicated a sample size of 629 per group is needed to insure with 80% power that the differences in success rates are within 5% of each other, assuming
  - a 95% two-sided confidence interval
  - underlying success rate per group is 92%
  - a randomized trial
  - no adjustments for dropouts
- for patients that are referred to a physician, the sponsor will need to obtain information through the referral facility
- the sponsor may be able to plan to have fewer sites in the non-referral arm; (e.g., if a historical control is used)
- if a historical control is used, the sponsor should demonstrate the similarities between the historical control population (and clinical trial procedures) to the current population (and to procedures in the current trial); any difference in population or procedures should be evaluated for their possible impact on the outcome of the trial; ideally, FDA would like a concurrent comparison between referring and non-referring physicians
- the sponsor would like to remove the teratogenicity study because the teratogenicity rate is so low
- the sponsor will maintain an audit of the physicians' compliance with the Medication Guide

Action Items:

- the sponsor should submit a proposal for the study described earlier including a sample size, referring physicians to get follow-up information on patients from referral facility (it built into the protocol); if the sponsor expects a lack of compliance, the sponsor can build this into the protocol
- the follow-up telecconference will be scheduled for Tuesday/Wednesday (meeting scheduled for Tuesday, August 29, 2000 @ 4:00PM if needed, for additional clarification (cancelled by sponsor)

/S/
Minutes Preparer

/S/
Concurrence, Chair

9/21/00

- Note to Sponsor: These minutes are official minutes.

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 11, 2000 **Time:** 3:30 – 4:00 PM **Location:** Parklawn; 13B-45

NDA 20-687 **Drug:** mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

FDA Attendees:

[redacted] Office of Evaluation III (ODEII; HFD-103)
[redacted] Project Management Staff, DRUDP (HFD-580)

External Participant:
Nancy Buc

Meeting Objective: To discuss the status of pending review issues pertaining to this drug product.

Discussion:

- the Black Box Warning should contain important safety or prescribing information that is not reflected elsewhere in the label. Contraindications, precautions, and teratogenic data are represented elsewhere.
- the Agency continues to stress the need for the patient to return to the physician's office on Day 3; this would help to establish the pattern for follow-up visits as recommended
- Medication Guide is not meant to stigmatize the drug product, but to fully inform the patient to allow her to participate knowledgeably in her own care.
- the MedGuide would be part of the approval and will be reviewed by the Center and the Agency. FDA will be sending the draft MedGuide to the sponsor the week of 8/28/00
- the Agency will be sending the sponsor comments to the distribution system and Exhibit E the week of 8/28/00
- the sponsor should propose Phase 4 protocols including the audit process to assess physician compliance with the physician qualification requirements (diagnosis ectopic pregnancy, date a pregnancy, and skills to perform surgical termination of pregnancy or referral to facility with those skills) in order for the Agency to review and comment
- the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners
- the Agency accepts the proposed qualification requirements the physician must meet before obtaining the drug product
- the sponsor agrees to restrict the distribution to qualified physicians
- the sponsor does not agree that the product should be approved under Subpart H; the Agency considers the drug is for a serious condition, unwanted pregnancy, for which this product provides a meaningful therapeutic benefit over existing therapies, avoidance of surgery.
- the Agency would like to have an agreement from the sponsor for the approval under the restricted distribution under Subpart H

- the sponsor plans to use the old production lot for first marketed product
- the sponsor would like to request that DDMAC waive pre-clearance requirements of promotional materials that are a condition of Subpart H approval
- the Agency requests the outstanding chemistry information be submitted by 8-31-00; included in that response are the response to the 483 and the stability data
- the Agency would request the sponsor send in Phase 4 commitment proposals for review

Action Items:

- FDA to send sponsor draft MedGuide and comments regarding the distribution system and Exhibit E the week of 8-28-00
- Sponsor to submit revised label and Phase 4 protocols by the end of August. Ms. Buc will discuss with her clients Subpart H approval and respond. (The sponsor revised submission date to 9-5-00, to respond to all outstanding issues, including MedGuide and revised Exhibit E.)

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: August 9, 2000 **Time:** 2:00 – 2:30 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** Mifepristone 200 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status

Meeting Chair: [redacted]

FDA Attendees:

[redacted] Office of Evaluation III (ODEII; HFD-103)
Project Management Staff, DRUDP (HFD-580)

External Participant:
Nancy Buc

Meeting Objective: To discuss the status of pending issues pertaining to this drug product.

Discussion:

- the Population Council is in the process of writing a letter responding to the pharmacology, MedGuide, and the home-se issue
- the sponsor needs FDA clarification regarding Phase 4 study proposal comparing the results of the referring physicians versus the non-referring physicians to evaluate patients outcome
- the purpose of this study is to assure that the information gained from this study would be comparable to the clinical trial, it is necessary to measure the following items: medical abortion failure rate, Day 14 return rate, and complication rate (i.e., transfusion, hospitalization, surgery for bleeding, surgery for abortion, infection rate); with a low complication rate (1%), sponsor should calculate sample size based on change ≤5% for example (120 patients approximately) to give reassuring data; the sponsor and the Agency have not yet agreed on a percentage
- the sponsor is concerned that surgeons would do the surgical abortion quicker than a non-surgeon and would make the results of the study change
- the sponsor has planned intervention plans if the study results find problems between referral and non-referral physicians (education, seminars)
- the sponsor needs to build a protocol that would take into consideration the timing that a surgeon can perform a surgical abortion
- the sponsor needs to contact physicians that would be interested in participating in the study and make sure that all steps are followed to ensure patient/physician confidentiality
- the sponsor can collect intermediate data to locate any problems before completing the study
- the sponsor believes that there will be more complete data from the non-referral physicians because they will have patient information; this can be built into the protocol
- the sponsor will propose a protocol trying to address all issues that could occur during that study

- both the Agency and the sponsor agree that it is important for the patient to return to the physician on Day 14 to ensure the procedure is complete
- the sponsor will propose a plan to study the pregnancy outcomes of the referral versus the non-referral physicians; the sponsor agrees to supply information regarding the patients who remain pregnant after the medical abortion fails, but the sponsor would like to ensure patient confidentiality and will propose a way to keep patient information confidential
- the tradename review is not complete, but the Office finds the name is acceptable due to direct distribution
- the FDA is still discussing the need to audit the patient agreement for compliance; the sponsor would like to avoid any public uproar regarding privacy; the sponsor needs to propose a way to audit the patient agreement without having a public uproar regarding this matter
- the FDA would propose a Day 3 return with a 4 hour observation in order to return home; the sponsor does not agree with this but understands the FDA's position
- the sponsor needs to add information regarding the chance of malformation with the use of misoprostol; the sponsor does not agree because in their study they had no incidence of malformation
- the sponsor believes that having a Black Box Warning is not necessary because of opposition of this drug and adding the risk of malformation may push patients to receive a surgical abortion when it may not be necessary; the Agency has added this information to the patient agreement because the Agency feels that there "may be a risk"; the Agency will review this information and comment further to the sponsor
- the sponsor is concerned with what would happen if the study results are not what they expected; the Agency would review the information accordingly and determine the cause of the differences, if any
- the Agency wants this information studied to ensure the safety of the patients versus numbers

Action Items:

- FDA will supply the sponsor with a draft MedGuide and Exhibit E comments
- The sponsor will submit draft labeling, Phase 4 proposals, and deficiency from inspection
- [redacted] will call Nancy Buc on 8-11-00 regarding the Black Box Warning

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: June 23, 2000 **Time:** 11:20 – 11:30 am **Location:** Parklawn, 17B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council/Danco

Type of Meeting: Guidance – meeting package contents

External Participant:

FDA Participant and Meeting Recorder: Division of Reproductive and Urologic Drug Products (HFD-580)

Meeting Objective: To request a timeframe for the submission of the background document from the sponsor for the upcoming July 19, 2000 meeting with FDA.

Discussion:

- , on behalf of Population Council, was informed that the following information was left in a voice-mail to Sandra Arnold, Population Council
- the following information should be included in the meeting package:
  - Update on status of CMC issues
  - Revised distribution system for this product
  - Revised labeling for this product
  - Update on status of the Phase 4 commitments
- indicated that this would be a burden since they were planning to only prepare comment for discussion at the upcoming meeting
- was reminded and confirmed that FDA has not had a sponsor update or revision of the distribution system since the January 2000 submission
- FDA has since then provided the sponsor with comments in the February 18, 2000 letter, as well as more recent recommendations for physician qualifications in the facsimile sent on June 1, 2000 following our teleconference on that date outlining those recommendations; comments regarding the proposed label have been provided to sponsor in the June 19, 2000 Information Request letter
- accordingly, to ensure progress with the review of this application and for the purposes of the upcoming meeting, revisions for both the distribution system and the labeling are required in the meeting package; only then will FDA be able to make substantial comments and provide feedback to the sponsor during the upcoming meeting
- it is critical to get this meeting package as soon as possible

Decisions made:

- None

Action Items:

- Danco to inform FDA of timing for submission of meeting package for July 19, 2000 meeting

/S/

Minutes Preparer and Chair

Teleconference Minutes

Date: June 19, 2000 **Time:** 9:30 – 9:45 am **Location:** Parklawn, 17B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council/Danco

Type of Meeting: Guidance – CMC

FDA Meeting Chair: [redacted]

External Chair: [redacted]

FDA Attendees:

[redacted], ONDC @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

[redacted], Project Management Staff, DRUDP (HFD-580)

External Participant:

[redacted], Danco

[redacted], Manufacturing, Danco

Meeting Objective: To discuss Danco's proposal to submit an upcoming CMC amendment to the pending NDA. (Attached facsimile was sent to [redacted] prior to this teleconference.)

Discussion:

- Danco indicated that several changes have been implemented at the factory including the validation process with 10-batch validation; these changes will be described and included in the upcoming amendment
- The Chinese facility inspection has been scheduled for July 24 – 28, 2000
- [redacted] will discuss the outstanding issues with the inspector prior to the inspection; one issue to verify is assurance that the process validation allows for the changes in the method; Danco confirmed that the additional 10 batches were run for validation in July and August 1999, prior to the last inspection in October 1999
- Over a total of [redacted] batches have been made to date
- [redacted] was conducted to verify Form 1

Decisions made:

- None

Action Items:

- Danco to submit CMC amendment by June 23, 2000

/S/
Minutes Preparer

/S/
Concurrence, Chair

Teleconference Minutes

Date: June 7, 2000 **Time:** 4:30 – 4:50 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Discussion of Press coverage

Meeting Chair: [redacted]

External Lead: [redacted]

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Office of Drug Evaluation III, Center for Drug Evaluation and Research (CDER), FDA

[redacted] Project Management Staff, Division of Reproductive and Urologic Drug Products (HFD-580)

External Attendees:

[redacted], The Danco Group
Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To clarify FDA comments and recommendations from the June 1, 2000 teleconference, to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.

Discussion:

Restricted Distribution

- FDA clarified with Population Council, Danco and Ms. Buc that the sponsor understood that a public registry of physicians was not proposed by FDA; rather, the FDA has proposed qualifications for physicians to ensure that recipients of the drug product are adequately trained for the safe use of this drug product; the sponsor's proposal for a distribution system, submitted in response to the approvable letters, only provided for the physical handling of the drug product; thus, in keeping with the recommendations of the July 1996 Advisory Committee and in order to advance the review of this application FDA provided recommendations for sponsor's consideration; sponsor concurred that this was also their understanding of the FDA proposals
- today's Press coverage described a "public registry" implying that qualified physicians could be readily identified and the list of those physicians could be publicly available; Population Council and Danco stated that their public statements only described the FDA recommendations as "more restrictive than expected" and that they did not provide any information about a public registry

- FDA asked sponsor to consider addressing the misinformation in the Press regarding this product; sponsor stated they were willing to consider correcting these misstatements and would get back to FDA Thursday, June 8 or Friday, June 9, 2000

Communications with the FDA regarding review of application

- public communication of the negotiation processes related to this drug application review can hamper the collaborative efforts put forth thus far between FDA and sponsor; FDA has not provided any information regarding the review of this application to the public or Press
- open, confidential communication between the FDA and the sponsor is necessary to continue making progress on the review and approval of this application as there are many areas remaining on which to reach agreement; the sponsor agreed that these were their goals as well; labeling recommendations will be provided by mid-June; sponsor will respond to FDA recommendations for qualifications of physicians by June 23
- FDA proposed that sponsor request a face-to-face meeting to continue discussion in early July; sponsor will make this meeting request through [redacted]

Decisions made:

- continue discussions of review issues in face-to-face in early July

Action Items:

- Population Council to inform FDA by June 9 of its intention to correct the misrepresentation regarding a public physician registry
- FDA to provide labeling revisions to sponsor in mid-June
- Population Council to provide responses to FDA proposed criteria for physician qualifications by June 23
- Population Council will request a meeting with [redacted] in early July and provide a package with a proposed agenda, questions and any relevant information for FDA consideration prior to this meeting
- FDA to provide copy of teleconference minutes to sponsor within 30 days

[redacted] /S/
Minutes Preparer

[redacted] /S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: June 1, 2000 **Time:** 1:00 – 1:30 pm **Location:** Parklawn, 13B-45

NDA 20-687 **Drug:** mifepristone **Indication:** medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Advice

Meeting Chair: [redacted]

External Lead:

Meeting Recorder: [redacted]

FDA Attendees:

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

External Attendees:

Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

Meeting Objective: To convey FDA comments and recommendations regarding the proposed restricted distribution, revised labeling and requested Phase 4 protocols for this application.

Discussion:

Phase 4 protocols

- the proposed protocols to address the Phase 4 commitments described in previous regulatory letters are to be submitted to FDA by August 1; sponsor expects to submit these protocols before August 1

Restricted Distribution

- a Subpart H requirement for this drug product continues to be under discussion in the Center; feedback may be available for sponsor regarding the FDA recommendation for Subpart H by the end of June 2000; a Subpart H requirement gives FDA authority to ensure compliance with restricted distribution
- if this product is approved not under Subpart H, a voluntary restricted distribution would still be necessary to assure adequate physical tracking and audit of the product and to assure that qualified physicians are certified to receive the product; sponsor's proposed distribution for physically tracking the product was proceeding in the right direction

- the following are additional FDA recommendations for criteria to assure the adequacy of qualifications for physician recipients (these criteria apply whether Subpart H is a condition for approval or whether there would be a voluntary restricted distribution system):

Proposed Restricted Distribution System for NDA 20-687

Qualifications for Physician Recipients:

1. Must be licensed to practice medicine in the state to which the drug is shipped.
   - acceptable documentation:
     - copy of valid physician's license

2. Has been trained to and is authorized by law to perform instrumental pregnancy termination (vacuum aspiration and D&C)
   - acceptable documentation:
     - sponsor to propose; self-attestation is discouraged

3. Has been trained to and has the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination.
   - acceptable documentation:
     - sponsor to propose; self attestation is discouraged

4. Has satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications.
   - acceptable documentation:
     - sponsor to propose curricula for review by FDA; sponsor to propose certification tracking system linked to the distribution system

5. Has continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or within one hour drive from the treatment facility.
   - acceptable documentation:
     - a signed letter by the Chief Medical Officer on the medical facility's stationary stating that the facility is properly equipped; sponsor to propose other acceptable documentation

Labeling recommendations

- revisions are being made to simplify the label and make it more effective for the clinician to use; revised labeling should be available to sponsor by mid-June
- FDA is proposing to delete the specific detailed references of the French data in the physician label to include only the most relevant data for clinician's to reference; inclusion of ranges that include the French data may be acceptable
- the Black Box Warning will remain in the label
- FDA recommends that the label should include the criteria that the patient must remain within one hour of an emergency medical facility to receive this product

- the WARNINGs section will include information about changes in bleeding and the need to confirm the loss of pregnancy in a followup visit
- FDA recommends deleting the [redacted] WARNING regarding the use of mifpristone with [redacted] since this product is not available for use in the United States
- FDA recommends that the misoprostol dose be given at a Second Visit in the clinic and that the patient must be observed for 4 hours post misoprostol as was studied in the clinical trials [redacted]
- FDA is recommending that the restricted distribution qualification requirements be listed in the HOW SUPPLIED section of the label for who would be eligible to receive the drug product
- although not a scheduled drug product, the label should emphasize the need to keep this product locked in a cabinet to assure the physical security and tracking of this product
- FDA will propose several revisions to the Patient Agreement Form; the patients will be required to initial each statement to assure an understanding and agreement of the information discussed; duplicate copies should be made so that the patient, medical record and distribution system are all assured to receive a separate copy of the Patient Agreement Form
- the labeling will refer to qualified recipients as physicians or doctors rather than "health care providers" to assure that only qualified physicians receive the drug product and assume the responsibilities under the distribution system; physician assistants and other health care professionals would not be qualified to receive this drug

Decisions made:

- further discussions between FDA and sponsor is needed before the action date for this application

Action Items:

- FDA to fax the list of Proposed Restricted Distribution System for NDA 20-687 (Qualifications for Physician Recipients) to sponsor (*NOTE: fax was sent by 2:00 pm June 1, 2000*)
- FDA to provide labeling revisions to sponsor in mid-June
- Population Council to provide responses to FDA proposed criteria for physician qualifications by mid-June
- Following reciept of FDA proposed labeling, Population Council will provide a request for a meeting and provide a package with proposed agenda, questions and any relevant information for FDA consideration prior to a meeting
- FDA to provide copy of teleconference minutes to sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: May 19, 2000 **Time:** 8:45-9:00 am **Location:** Parklawn; 18B-09

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Teleconference

Meeting Chair: [redacted]

External Lead: Sandra Arnold

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)

[redacted] Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Sandra Arnold, Population Council

Nancy Buc, Buc and Beardsley

Meeting Objective: To discuss proposed distribution system with the sponsor and request that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product. To request Phase 4 Commitment summary protocols for review during this review cycle.

Discussion:
Distribution system:

We are actively reviewing the proposed labeling and the distribution system; final comments or decisions are pending, however, there are several issues to be addressed:

- The proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.
  - Patients must be assured that providers will be qualified physicians who are trained in the surgical abortion procedure and currently providing that service. Providers must be available to manage any emergency complications such as hemorrhage and incomplete abortions. Referral to a hospital emergency department by ambulance is not acceptable.

- Appropriate provider qualifications must be specified in the distribution plan, and the sponsor will be required to audit the distribution system to assure that providers meet appropriate qualifications.

- Provide us with acceptable, auditable criteria, e.g., that they be licensed physicians. Other criteria may include Board certification (OB/GYN or FP?), certification of training &/or experience, hospital credentials/privileges, facility certification, documentation of number of procedures performed, etc.; designate how you will audit the designated criteria.

- Indicate how you will assess compliance by providers and include a provision to discontinue from the distribution plan any provider who does not comply with the requirements.

Phase 4 commitments

The requested Phase 4 commitments are not optional and are requirements for approval. Summary protocols for these commitments, need to be submitted by August 1 to allow for review prior to approval.

Action Items:

- Sponsor to provide proposal for appropriate provider qualifications to ensure safety and appropriate follow-up care for patients
- Sponsor to submit Phase 4 summary protocols for review by August 2000

/S/
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: April 26, 2000 **Time:** 11:44 – 12:00 PM **Location:** Parklawn; 17B-45

NDA 20-687 **Drug:** mifepristone, 600 mg

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Guidance

FDA Attendees:

Division of New Drug Chemistry II (DNDCII) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

– DANCO Group (CRO for Population Council)

Meeting Objective: To communicate information to the sponsor regarding the methods validation package and clarification on the Phase 4 commitment in the February 18, 2000 approvable letter.

Decisions made:

Regarding Methods Validation Package

- the following information should be provided in the methods validation package:
  - the sponsor should prepare four sets of samples (two for the labs and two for back-ups)
    - include the reference standard for the drug substance from both Shanghai Hua Liau and Rousell
  - a list of the composition of the drug product
  - specifications for both the drug product and drug substance
  - a description of the methods with the method validation data
  - material safety data sheets

Regarding Phase 4 commitments

- the sponsor should submit a summary of the proposed protocols to the Division for review
- the summary protocols should include all the information outlined in the February 18, 2000 approvable letter and in the sponsor's letter dated September 16, 1996
- these summary protocols must be reviewed and approved by the Division prior to approval of this product

Action Items:

- fax meeting minutes to the sponsor within 30 days

/S/

Minutes Preparer

/S/ 4/28/00

Concurrence, Chair