The Population Council

Center for
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/S/

ORIGINAL

/S/ 10-1-96

/S/ 9/3/96

September 26, 1996

5NC

———— 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
ACTION:
LETTER /S/ N.A.I.
DATE
CSO INITIALS

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

Dear ————

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 ————, 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

APPEARS THIS WAY
ON ORIGINAL

MIF 006501

ORIGINAL

**Date:** June 18, 1996 **Time:** 8:00-10:00 **Location:** Parklawn 14-56

**NDA:** 20-687 **Drug Name:** Mifepristone

**External Participant:** The Population Council

**Type of Meeting:** 90 day meeting

**Meeting Chair:** [redacted] **External Participant Lead:** Ann Robbins, Ph.D.

**Meeting Recorder:** [redacted]

**FDA Attendees:**

[redacted] Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)
[redacted], Medical Officer (HFD-580)
[redacted] (HFD-580)
[redacted] (HFD-820)
[redacted] (HFD-580)
[redacted] (HFD-580)
[redacted] (HFD-580)
[redacted], Biopharmaceutics Review Officer (HFD-870)

**External Constituaents:**

Ms. Sandra Arnold
Wayne C. Bardin, M.D.,
Mr. James Boynton
Ms. Margaret Catley-Carlson
Ann Robbins, Ph.D.

**Meeting Objectives:**

To discuss the status of the NDA review and the upcoming Advisory Committee Meeting.

**Discussion Points:** See below.

**Decisions Reached:**

- Change in Classification from Standard to Priority
  - The Division would like to complete the review and deliver an action letter soon after the Advisory Committee meeting (Scheduled for July 19, 1996). The target goal date will be September 14, 1996.
  - Because the target date is September, the Population Council will submit a Safety Update at the end of June. This will include some preliminary safety data from the U.S. trials.

- Starting Material

  - The Population Council acknowledged the Agency's need for more information regarding the starting material. They stated that they are currently attempting to negotiate with Roussel Uclaf on this point but have not yet received any further information. At this time they are unable to say whether they will be able to obtain more information regarding this or not.

  - The Population Council will be able to submit their new manufacturer's DMF which would contain satisfactory information on the starting material for the bulk drug early fourth quarter of this year, but will not have the rest of the data until the first quarter of next year.

  - The sponsor was told that if a new DMF were submitted by a new manufacturer, they would be required to show that the to-be-marketed formulation was identical to the clinically tested formulation with respect to identity, purity, and dosage (e.g., absorption etc.). Additionally, the sponsor would be required to show bioequivalence between the clinically tested formulation and the to-be-marketed formulation. The necessity of an in vivo bioequivalence study will be assessed with regard to changes in manufacturing site, procedure and equipment, as well as formulation composition. If a waiver of the in vivo bioequivalence study is granted, then appropriate comparative dissolution studies will be sufficient to establish the bioequivalence of the clinically tested formulation and to-be-marketed formulation. The sponsor noted that they would not be able to complete the necessary studies within the next six months.

  - It was suggested that if the sponsor was unable to supply the required information, an Approvable letter may still be a possibility.

- Status of Pending NDA issues

  - The sponsor noted that the Division of Biopharmaceutics had communicated a request for dissolution data on their drug product. They will be in France to hold discussions with Roussel Uclaf on Thursday, and request that a formal letter from the FDA outlining the Biopharmaceutic request be faxed to them prior to their meeting with Roussel, they further requested the chemistry comments also be faxed as a formal letter at the same time.

  - The sponsor noted that the U.S. trials were completed in the Fall of last year, however the 100% audit that they have elected to do on the data is not expected to be complete until July. They assert that the safety and efficacy data in the U.S. trials are similar to those in the European trail.

  - The sponsor was told that the Establishment Evaluation Request had been returned and had been found acceptable.

- The sponsor stated that the clinical trials were scheduled to be audited by DSI on June 24, 1996. The sponsor has just completed their own audit of the clinical sites and have left for the auditors a clear paper trail of what they have done, they have also included English translations of all French documents. The sponsor noted that they have not had time to see if the data from their audit might change any of the information in the NDA.

- The sponsor was told that review of the proposed labeling was not yet complete. The sponsor noted that the Division of Biopharmaceutics had given them their labeling revisions, and these revisions would be submitted as new draft labeling soon.

- Advisory Committee

  - A draft agenda was reviewed and the time allocations for presentations were discussed.

  - The Agency told the sponsor that a venue had not yet been decided upon, however there was one good prospect. It was suggested that the sponsor come the day before the meeting to view the site of the meeting.

  - The sponsor was told that the Division planned only to make opening introductions, and that we would not be discussing the concomitant use of Cytotec with their product. It was agreed that the Agency would address the fact that this NDA's safety and efficacy rests primarily on foreign data, but that there was precedence for this, the Division will discuss appropriate wording with CDER management, and obtain specific examples of other NDAs approved mainly with foreign data.

  - The sponsor stated that they would discuss preliminary safety data from their U.S. trials but would not address efficacy. Further they will make clear that the U.S. data presented have not yet been reviewed by the Agency.

  - The sponsor asked if Roussel Uclaf would be named in any FOIable documents. The Agency responded that an Approvable letter would not be FOIable, however if the sponsor received an Approval letter Roussel Uclaf would be named in the review.

  - The sponsor noted that they still have a large stock of unembossed mifepristone tablets left after the trials. They asked if they could use these for other clinical trials. The sponsor asked for clarification of the difference between compassionate use INDs and Treatment IND's. The Agency will send the appropriate sections of the CFR to the sponsor after this meeting. The sponsor noted that they do not plan to provide this drug for patients requesting it to terminate pregnancies.

  - The discussion of Cytotec and the proposed drug label was discussed. It was noted that Cytotec's label would not need to be amended. It was suggested that the label be for a combined product since Cytotec was not approved for use in pregnant women. The Division of Biopharmaceutics suggested that kinetics in pregnant women be examined post-approval.

- The sponsor was asked when they expected to be able to supply mifepristone to the U.S. population. The sponsor replied that they expected to be able to market a this product in about twelve months.

**Unresolved Issues:** None

**Action Items:** The Agency will Fax two letters to the sponsor before 3:00 pm on June 20, 1996. These will contain the chemistry information requests, and the biopharmaceutics dissolution data request.

The sponsor will submit an updated Safety Update which will include preliminary safety data from the U.S. trials by the end of June.

/S/ 9/16/96
Signature, minutes preparer

/S/
Concurrence, Chair

cc:
NDA Arch
HFD-
HFD-
HFD-
HFD-
HFD-

No Response:

Meeting Minutes

APPEARS THIS WAY
ON ORIGINAL

OCT 1 1996

NDA 20-687
Mifepristone

The Population Council
September 26, 1996

Medical Officer's Review of Amendment 004 Dated September 16, 1996

I. Submission dated September 16, 1996 contains a summary report of the serious adverse events that occurred during the United States clinical trials conducted under protocols 166A and 166B. All of these reports were previously submitted in IND ——' and summarized in the United States Safety Data submitted by the sponsor July 14, 1996 to NDA 20-687.

This report was previously reviewed and evaluated ( Please see Medical Officer's Review dated August 29, 1996 of the United States Safety Data dated July 14, 1996). A comparison of the frequency of these serious adverse events reported in the United States trials and those reported in the pivotal French studies included in the NDA is provided below.

COMPARISON OF SERIOUS ADVERSE EVENTS IN THE
U.S. CLINICAL TRIALS AND NDA PIVOTAL TRIALS

| | United States | French |
|---|---|---|
| No. Subjects enrolled | 2121 | 2480 |
| No. Of hospitalizations | 26 (1%) | 21 (1%) |
| No. Of transfusions | 4 (<1%) | 4 (<1%) |
| No. Of subjects with hemorrhage | 41 (2%) | 52 (2%) |
| Surgical intervention for bleeding | 32 (2%) | 15 (1%) |

The incidence of hemorrhage, transfusions, and hospitalization was similar in the United States studies and the French studies. The higher incidence of surgical intervention for bleeding in the United States trials may be explained by the initial inexperience of the United States clinicians in providing medical abortions. Investigators in the United States trials have indicated that there was a learning curve associated with the treatment of bleeding during the trials.

II. This submission also contains a response to FDA's letter of August 22, 1996 to the sponsor regarding phase IV studies.

A. The sponsor intends to monitor the distribution and credentialing system.

B. The sponsor proposes to investigate treatment failures among a representative sample of providers for a mutually agreeable period of time.

C. The sponsor will examine data sources from central registries of Mifepristone users in Europe to determine what can be learned about multiple use. In addition, the sponsor will attempt in future studies in the United States to develop a cohort of women who report more than one use of the regimen and agree to be followed.

D. The sponsor's response to ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not is the same as "B." above.

E. The sponsor will submit analyses of the safety and efficacy data on users of the regimen who are under age 18, over age 35, and smokers. [ Study FF/92/486/24 included 144 subjects who were over 35 years of age.] In addition, data on women under 18 or over 35 years of age and those who smoke will be collected from a sample of women.

F. The sponsor will instruct their distributor to request providers to report treatment failures in women who decide to continue their pregnancy. The provider will ascertain which of these women are agreeable to follow up to document the health of children born of such pregnancies. In addition, spontaneous reports of live births of children exposed to Mifepristone in utero will be investigated.

Comment: FDA reminded the sponsor of their commitments to perform these phase IV studies in a letter to them dated September 18, 1996.

/S/

Concur /S/ 10/1/96

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VIA FEDEX

September 16, 1996

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

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

Dear ———

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

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

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

Population Council

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

Sincerely,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

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~~NDA SUPP AMEND~~

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REVIEWS COMPLETED
CSO ACTION: N.A.I. MEMO
9/18/96
CSO INITIALS DATE

VIA FEDEX

September 16, 1996

REC'D
SEP 17 1996
HFD-580

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

Ann Robbins

Ann Robbins, Ph.D.
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APPEARS THIS WAY
ON ORIGINAL

# APPENDIX 1

# SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED IN PROTOCOL 166A/B

## Introduction

This internal Population Council report was generated in preparation for the upcoming Mifepristone NDA 20-687 advisory committee meeting on July 19, 1996. The goal was to summarize all serious adverse events (SAEs) that occurred during the conduct of Protocol 166A/B. SAEs are defined as those events reported to the Council from the clinics which the Council then reported to the FDA on Medwatch forms. All of these SAEs reports have been previously submitted to the FDA in ~~~~ , as well as documented in NDA 20-687.

## Results

The data relevant to SAEs have been summarized in the following three tables. Table 1 lists each participating clinic by clinic number, principal investigator name, location and type of clinic. Table 2 identifies, in chronological order of occurrence, each subject for whom a SAE was reported to the FDA on a Medwatch form. The nature of the adverse event(s) is recorded as well as the need for a dilatation and curettage (D&C) or aspiration, intravenous fluids, transfusion or hospitalization. When available, the subject's duration of amenorrhea and ethnicity is provided. Finally, the IND submission number and date the Medwatch form was submitted to the IND are listed.

The summary of Table 2 indicates that a total of 52 subjects had at least one SAE. There was more than one adverse event reported for most subjects on the Medwatch forms. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least 4 subjects are listed in the Summary of Table 2.

These serious adverse events resulted in the hospitalization of 26 subjects. Four subjects received transfusions. A total of 28 subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of 34 subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen (15) subjects received methergine or oxytocin for treatment of bleeding, although 11 of these subjects eventually had a surgical procedure.

The Drug Surveillance Department of Roussel Uclaf maintains a database of all serious adverse events associated with mifepristone for any medical use. At the request of Roussel, the Council sends to them information on all SAEs from the U.S. clinical trials that were reported to the FDA. Roussel assigns an "International Drug Surveillance Number" (IDSN) to each SAE and then provides a medical code for the reported SAE. These SAEs from the U.S. trial are thus captured in Roussel's database and are included in their quarterly reports of international SAEsa associated with mifepristone use. The SAEs from the Council's U.S. study have been reported in the NDA by this IDSN, in order to correspond to the report numbering system of other SAEs included in our NDA from international use of mifepristone in clinical trials and during post-marketing surveillance. However, this has caused some confusion in identification of subjects in the U.S. clinical trial for three reasons: 1) one subject may be assigned more than one IDSN by Roussel, depending upon how many adverse events occurred, since the IDSN is associated with an adverse event, not a subject; and 2) the medical code for the SAE assigned by Roussel may not precisely correspond to the description of the SAE as reported on the Medwatch form submitted to the FDA by the Council and 3) Roussel has made some mistakes in their coding of subject's identification. The purpose of Table 3 is to clarify the relationship between a subject in the U.S. trial and the IDSN(s) assigned to that subject by Roussel. In Table 3, each subject with an SAE in the Council's trial is identified and the IDSN(s), as assigned by Roussel, that are associated with that subject are listed. The medical code assigned by Roussel for the SAE(s) of each subject is also included.

For four subjects in the U.S. trial, Roussel has not yet assigned an IDSN or medical code (subject 123, clinic 01; subject 076, clinic 03; subject 070, clinic 02; and subject 159, clinic 01). The location in the NDA of the line listing of the SAE, as identified by the IDSN, is also indicated on Table 3. Line listings of all of the SAEs in the U.S. clinical trial were included in either the original NDA submission of March 14, 1996 (Volume 1.66, p. 32) or the NDA Safety Update Report of June 20, 1996 (Volume 3.2, p. 10).

Comparison of U.S. trials and pivotal NDA trials

It is not possible to make a complete comparison of the serious adverse events reported in the U.S. trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the U.S. trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the U.S. and NDA pivotal studies can only be made with the serious adverse events reported from these 52 U.S. subjects who had a Medwatch report, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire U.S. database. However, some general comparisons can be made. The total number of subjects enrolled in U.S. Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the U.S. trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by 41 subjects in the U.S. studies who required a Medwatch report. In the NDA pivotal studies, 52 subjects reported metorrhagia or excessive bleeding, which was categorized as severe in 21 subjects. However, the manner in which the bleeding was treated differed in the two studies. In the U.S. trials, 32 of the 34 surgical interventions (D&C or aspiration) reported on the Medwatch forms were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of 15 subjects

received surgical interventions for bleeding. The greater number of surgical interventions by U.S. investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the U.S., but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The U.S. investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were 5 cases of hypotension reported on Medwatch forms, although blood pressure readings were given for only 2 of these subjects. There were 7 cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia on the Medwatch forms for U.S. subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported on Medwatch forms of the U.S. subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the U.S. database.

Conclusions

The SAEs reported during the U.S. trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the U.S. trials may be explained by the initial inexperience of U.S. clinicians in providing medical abortion. Investigators in the U.S. trial have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies. In summary, the current comparison of SAEs between our U.S. trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of U.S. settings.

## Table 1

## Clinics in Population Council US Studies Protocol 166A/B

| Clinic Number | Investigator Name | Location | Type of Clinic* | Protocol A or B |
|---|---|---|---|---|
| 01 | Mishell | Los Angeles, CA | University Hospital | A |
| 02 | Haskell | Des Moines, IA | Planned Parenthood | A |
| 03 | Poppema | Seattle, WA | Other | A |
| 04 | Tyson | Burlington, VT | Planned Parenthood | A |
| 05 | Blumenthal | Baltimore, MD | University Hospital | A |
| 06 | Borgotta | White Plains, NY | Planned Parenthood | A |
| 07 | Malloy | Atlanta, GA | Other | A |
| 08 | Rothenberg | Shrewsburg, NJ | Planned Parenthood | A |
| 21 | Poindexter | Houston, TX | Planned Parenthood | B |
| 22 | Vargas | Denver, CO | Planned Parenthood | B |
| | | | | |
| 24 | Westhoff | New York, NY | University Hospital | B |
| 25 | Nichols | Portland, OR | Other | B |
| 26 | Sheehan | San Diego, CA | Planned Parenthood | B |
| 27 | Dean | St. Louis, MO | Other | B |
| 28 | Creinin | Pittsburgh, PA | University Hospital | B |
| 29 | Sogor | Cleveland, OH | Other | B |

* Other = Clinic or Private Office.

## Table 2

## IND Safety Reports (Med Watch) Submitted to [redacted]

| Patient No. | Clinic No. | Adverse Event | D&C/ Asp. | Meth./ oxy. | IV Fluids | Trans-fusion | Hosp. | DA | Race | IND No. and Date |
|---|---|---|---|---|---|---|---|---|---|---|
| (005) | 22 | Hemorrhage | X | | X | X | X | 63 | | 107 11/21/94 |
| 036 | 02 | Hemorrhage Vomiting Fainting | X | | X | | | 44 | | 108 12/01/94 |
| 033 | 02 | Vomiting Diarrhea Dehydration | | | X | | | 49 | | 108 12/01/94 |
| 027 | 02 | Hemorrhage Cramping | X | | | X | X | 53 | East Asian | 109 12/07/94 |
| 042 | 02 | Hemorrhage Cramping Dizziness | X | | X | | X | 51 | Cau-casian | 109 12/07/94 |
| [redacted] (057) | 01 | Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia | X | | X | X | | 44 | | 110 12/20/94 |
| 015 | 25 | Hemorrhage Cramping | X+ | | | | | 46 | | 113 01/18/95 |
| 012 | 25 | Hemorrhage Cramping | X | | | | | 49 | | 113 01/18/95 |
| 061 | 01 | Hemorrhage Weak Nausea Pale & Cold | | | X | | | 57 | | 113 01/18/95 |
| 076 | 02 | Hemorrhage Vomiting Cramping Chlamydial infection | | | | | | | | 113 01/18/95 |
| 033 | 03 | Hemorrhage Syncope Pallor | X | X | | | | 52 | | 113 01/18/95 |
| 022 | 25 | Hemorrhage Cramping Feeling Faint | X | | X | | X | 56 | | 114 01/23/95 |
| 050 | 03 | Hemorrhage Dizziness Postural Hypotension (BP 60/ palpable) | X | | | | X | 30 | | 114 01/23/95 |

## Table 2 (Cont'd)

| Patient No. | Clinic No. | Adverse Event | D&C/ Asp. | Meth./ oxy. | IV Fluids | Trans-fusion | Hosp. | DA | Race | IND No. and Date |
|---|---|---|---|---|---|---|---|---|---|---|
| 009 | 26 | Hemorrhage Cramping Syncope | X | | X | | X | 57 | | 115 02/07/95 |
| 062 | 01 | Hemorrhage Cramping | X | | | | X | 57 | His-panic | 118 02/15/95 |
| 107 | 01 | Vomiting Dizziness | | | X | | | | | 118 02/15/95 |
| 114 | 01 | Hemorrhage | X | X | | | X | 62 | His-panic | 118 02/15/95 |
| 123 | 01 | Hemorrhage Dizziness Headache | | X | X | | | 53 | | 118 02/15/95 |
| 037 | 04 | Hemorrhage | X | | X | | | 65 | | 118 02/15/95 |
| 109 | 01 | Hemorrhage Fever | X | | X | | X | 45 | | 119 02/17/95 |
| 116 | 01 | Chest Pain | | | | | X | | | 119 02/17/95 |
| 048 | 03 | Hemorrhage Tachycardia | X | | | | X | 51 | | 120 03/03/95 |
| 076 | 03 | Hemorrhage Cramping | | X | | | | | | 121 03/06/95 |
| 060 | 24 | Hemorrhage Hypotension Tachycardia | | | X | X | | 54 | | 122 03/10/95 |
| 017 | 23 | Hemorrhage Orthostatic Hypotension | X | X | X | | | 57 | | 123 03/13/95 |
| 070 | 02 | Gunshot | | | | | X | | | 123 03/13/95 |
| 030 | 23 | Hemorrhage Syncope Tachycardia Hypotension | X | | X | | | 52 | | 124 04/11/95 |
| 032 | 23 | Vasovagal reaction | | | X | | | | | 124 04/11/95 |
| 035 | 23 | Hemorrhage | | X | X | | | | | 124 04/11/95 |
| 037 | 23 | Hemorrhage Dizziness Shortness of Breath | X | X | X | | | 51 | | 124 04/11/95 |
| 081 | 26 | Hemorrhage Syncope/neck injury | X+ | | | | X | 51 | | 124 04/11/95 |
| 158 | 02 | Hemorrhage Weakness | X | X | X | | | 54 | | 125 04/19/95 |

## Table 2 (Cont'd)

| Patient No. | Clinic No. | Adverse Event | D&C/ Asp. | Meth./ oxy. | IV Fluids | Trans-fusion | Hosp. | DA | Race | IND No. and Date |
|---|---|---|---|---|---|---|---|---|---|---|
| 159 | 01 | Hemorrhage | X+ | X | X | | | 50 | | 125 04/19/95 |
| 036 | 27 | Pneumonia | | | | | X | | | 132 06/07/95 |
| 012 | 29 | Hemorrhage Cramping Faintness | X | | | | X | 53 | | 132 06/07/95 |
| 028 | 04 | Hemorrhage Dizziness | | X | | | | | | 132 06/07/95 |
| 075 | 04 | Nausea Dizziness | | | X | | | | | 132 06/07/95 |
| 004 | 28 | Hemorrhage | X | X | | | X | 55 | | 132 06/07/95 |
| 027 | 28 | Hemorrhage Vomiting Lightheaded | X | | X | | X | 50 | | 133 06/13/95 |
| 071 | 23 | Hemorrhage Vomiting Dizziness | X | | X | | X | 55 | Afro-Amer-ican | 136 07/18/95 |
| 030 | 28 | Hemorrhage | | | | | | | | 136 07/18/95 |
| 033 | 28 | Hemorrhage | X | | | | X | 46 | | 138 07/25/95 |
| 063 | 28 | Anxiety attack Depression Threatened suicide | | | | | X | 50 | | 139 07/28/95 |
| 147 | 27 | Viral meningitis | | | | | X | | | 141 08/04/95 |
| 074 | 28 | Hemorrhage Passed out | X | X | X | | X | 60 | | 143 08/09/95 |
| 088 | 28 | Hemorrhage (2 Med Watch reports) | X | X | X | | X | 62 | | 143 08/09/95 144 08/10/95 |
| 018 | 07 | Abdominal pain | X | | | | | 42 | | 145 08/15/95 |
| 019 | 07 | Hemorrhage | | | | | | | | 145 08/15/95 |
| 104 | 28 | Hemorrhage Cramping | X | X | X | | X | 62 | | 146 08/25/95 |
| 108 | 28 | Cramping Fever, tender uterus | X | X | | | X | 63 | | 147 09/01/95 |

## Table 2 (Cont'd)

| Patient No. | Clinic No. | Adverse Event | D&C/ Asp. | Meth./ oxy. | IV Fluids | Trans-fusion | Hosp. | DA | Race | IND No. and Date |
|---|---|---|---|---|---|---|---|---|---|---|
| 116 | 24 | Hemorrhagia<br>Cramping<br>Fever<br>Endometritis | X | | X | | | 61 | | 149<br>09/21/95 |
| 165 | 25 | Hemorrhage<br>Dizziness | X | | X | | X | 60 | | 154<br>11/02/95 |

## Summary of Table 2

| Total No. of Patients | Total No. of Clinics | Total No. of Adverse Events | Total Number of Treatments | | | | Total No. Hospitalized |
|---|---|---|---|---|---|---|---|
| | | | D&C/ Asp. | Meth./ oxy. | IV Fluids | Transfusion | |
| 52 | 13 | **Hemorrhage 41**<br>**Faint/Dizziness** 20**<br>**Cramping 14**<br>**Vomiting 06**<br>**Hypotension 05**<br>**Tachycardia 04** | 34 | 15 | 28 | 04 | 26 |

* Listed in chronological order as reported to the FDA.
+ Surgical procedure not reported on Med Watch form.
D&C/Asp = Dilatation and Curettage/Aspiration.
Meth/oxy = Methergine/Oxytocin.
Hosp. = Hospitalizations.
DA = Number of days of amenorrhea.
** includes fainting, feeling faint or lightheaded, dizziness, vasovagal reaction, syncope and passing out.

Table 3

**Correlation between Population Council Subject and Serious Adverse Event Coded by Roussel**

| Patient No. | Clinic No. | IDSN* | SAE** Coded by Roussel | Location in NDA Volume Page |
|---|---|---|---|---|
| 01 (005) | 22 | 199500076RU | Metrorrhagia<br>Anemia | Vol. 1.66 p.32 |
| | | 199500439RU | Metrorrhagia<br>Abdominal pain | Vol. 3.2 p.10 |
| 036 | 02 | 199500072RU | Metrohagia<br>Vomiting<br>Malaise | Vol. 1.66 p.32 |
| 033 | 02 | 199500442RU | Dehydration<br>Nausea<br>Vomiting<br>Diarrhea | Vol. 3.2 p.10 |
| 027 | 02 | 199500074RU | Abdominal pain<br>Anemia<br>Metrorrhagia | Vol. 1.66 p.32 |
| 042 | 02 | 199500075RU | Abdominal pain<br>Metrorrhagia<br>Anemia | Vol. 1.66 p.32 |
| (057) | 01 | 199500071RU | Metrorrhagia<br>Hypotension<br>Anemia | Vol. 1.66 p.32 |
| | | 199500440RU | Metrorrhagia<br>Hypotension<br>Headache | Vol. 3.2 p.10 |
| 015 | 25 | 199500066RU | Metrorrhagia | Vol. 1.66 p.32 |
| 012 | 25 | 199500067RU | Metrorrhagia | Vol. 1.66 p.32 |
| 061 | 01 | 199500068RU | Hypotension | Vol. 1.66 p.32 |
| 076 | 02 | 199500069RU | Urogenital Disorder | Vol. 1.66 p.32 |
| 033 | 03 | 199500070RU | Metrorrhagia<br>Syncope | Vol. 1.66 p.32 |
| | | 199500444RU | Metrorrhagia<br>Dizziness<br>Headache | Vol. 3.2 p.10 |
| 022 | 25 | 199500441RU | Abdominal Pain<br>Hypotension | Vol. 3.2 p.10 |
| | | 199500064RU | Metrorrhagia | Vol. 1.66 p.32 |

Table 3 (Cont'd)

| Patient No. | Clinic No. | IDSN* | SA** Coded by Roussel | Location in NDA Volume Page |
|---|---|---|---|---|
| 050 | 03 | 199500065RU | Metrorrhagia Postural hypotension | Vol. 1.66 p.32 |
| 009 | 26 | 199500077RU | Metrorrhagia | Vol. 1.66 p32 |
| 062 | 01 | 199500102RU | Metrorrhagia | Vol. 1.66 p.32 |
| 107 | 01 | 199500443RU | Vomiting Nausea Dizziness | Vol. 3.2 p.10 |
| 114 | 01 | 199500104RU | Metrorrhagia | Vol. 1.66 p.32 |
| 123 | 01 | NA*** | NA | Vol. 1.66 p.32 |
| 037 | 04 | 199500106RU | Metrorrhagia | Vol. 1.66 p.32 |
| 109 | 01 | 199500100RU | Metrorrhagia Fever | Vol. 1.66 p32 |
| 116 | 01 | 199500101RU | Chest pain | Vol. 1.66 p.32 |
| 048 | 03 | 199500140RU | Metrorrhagia | Vol. 1.66 p.32 |
| 076 | 03 | NA | NA | Vol. 1.66 p.32 |
| 060 | 24 | 199500139RU | Metrorrhagia Hypotension | Vol. 1.66 p.32 |
| 017 | 23 | 199500135RU | Metrorrhagia Postural Hypotension | Vol. 1.66 p.32 |
| 070 | 02 | NA | NA | Vol. 1.66 p.32 |
| 030 | 23 | 199500175RU | Metrorrhagia Syncope | Vol. 1.66 p.32 |
| 032 | 23 | 199500446RU | Syncope | Vol. 3.2 p.10 |
| 035 | 23 | 199500447RU | Metrorrhagia | Vol. 3.2 p.10 |
| 037 | 23 | 199500176RU | Metrorrhagia | Vol. 1.66 p.32 |
| 081 | 26 | 199500172RU | Metrorrhagia Syncope | Vol. 1.66 p.32 |
| 158 | 02 | 199500179RU | Metrorrhagia | Vol. 1.66 p.32 |
| 159 | 01 | NA | NA | Vol. 1.66 p.32 |
| 036 | 27 | 199500247RU | Pneumonia | Vol. 1.66 p.32 |

Table 3 (Cont'd)

| Patient No. | Clinic No. | IDSN* | SAE** Coded by Roussel | Location in NDA Volume Page |
|---|---|---|---|---|
| 012 | 29 | 199500248RU | Metrorrhagia | Vol. 1.66 p.32 |
| 028 | 04 | 199500249RU | Metrorrhagia | Vol. 1.66 p.32 |
| 075 | 04 | 199500448RU | Dehydration | Vol. 3.2 p.10 |
| 004 | 28 | 199500251RU | Metrorrhagia | Vol. 1.66 p.32 |
| 027 | 28 | 199500455RU | Metrorrhagia | Vol. 3.2 p.10 |
| 071 | 23 | 199500329RU<br><br>199500449 | Vomiting<br><br>Metrorrhagia<br>Dizziness | Vol. 1.66 p.32<br><br>Vol. 1.66 p.32 |
| 030 | 28 | 199500330RU | Metrorrhagia | Vol. 1.66 p.32 |
| 033 | 28 | 199500454RU | Metrorrhagia | Vol. 1.66 p.32 |
| 063 | 28 | 199500340RU | Depression | Vol. 1.66 p.32 |
| 147 | 27 | 199500342RU | Meningitis | Vol. 3.2 p.10 |
| 074 | 28 | 199500450RU<br><br>199500355RU | Metrorrhagia<br>Hypotension<br><br>Metrorrhagia<br>Hypotension<br>Anemia | Vol. 3.2 p10<br><br>Vol. 3.2 p.10 |
| 088 | 28 | 199500356RU<br><br>199500451RU | Metrorrhagia<br><br>Metrorrhagia | Vol. 3.2 p.10<br><br>Vol. 3.2 p.10 |
| 018 | 07 | 199500365RU | Abdominal pain | Vol. 3.2 p.10 |
| 019 | 07 | 199500366RU | Metrorrhagia | Vol. 3.2 p.10 |
| 104 | 28 | 199500452RU | Metrorrhagia<br>Uterine spasm | Vol. 3.2 p.10 |
| 108 | 28 | 199500375RU | Abdominal pain<br>Fever | Vol. 3.2 p.10 |
| 116 | 24 | 199500453RU | Metrorrhagia<br>Endometrial disorder | Vol. 3.2 p.10 |
| 165 | 25 | 199500427RU | Metrorrhagia<br>Malaise | Vol. 3.2 p.10 |

*IDSN= International Drug Surveillance Number.
**SAE = Serious Adverse Event.
***NA = Not available, not yet assigned by Roussel.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

AUG 22 1996

The Population Council
Attention: Ann Robbins, Ph.D.
1230 York Avenue
NEW YORK NY 10021

Dear Dr. Robbins:

Please refer to your pending March 18, 1996, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone 200 mg tablets.

As your are aware, during the meeting on July 19, 1996, members of the Reproductive Health Drugs Advisory Committee made several recommendations for additional studies of the regimen containing mifepristone and misoprostol to be conducted during Phase 4. The purpose of this letter is to reiterate these recommendations and to obtain your commitment to pursue these investigations as Phase 4 studies.

Please acknowledge the commitment to perform Phase 4 studies with the following objectives:

1. to monitor the adequacy of the distribution and credentialing system by determining, among other endpoints, the frequency of post-surgical complications;

2. to follow-up on the outcome of all women who have surgical abortion because of method failure;

3. to determine the long-term effects of multiple use of the regimen;

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

5. to study the safety and efficacy of the regimen in women under age 18, over age 35, and in smokers;

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

We look forward to discussing your proposals for these studies and are available to provide assistance in their design. For your information, the final protocols need not necessarily be submitted prior to our regulatory action on your application.

If you have any questions concerning these commitments, please contact [redacted], CSO at

Sincerely yours,

/S/

[redacted]

Division of Reproductive and Urologic
Drug Products (HFD-580)
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

FAXED 14 July '96

Fed Ex 15 July 96

Fax from Ann Robbins, Ph.D
Phone: 212-327-8748
Fax: 212-327-7678

| | |
|---|---|
| Number of Pages (including this sheet): | 12 |
| Send to Facsimile Number: | [redacted] |
| Date: | 14 July 1996 |
| Send to Company: | FDA,<br>Division of Reproductive<br>and Urologic Drug Products |
| Send to Person: | [redacted] |
| Subject: | U.S. Safety Data |

Dear [redacted]

As requested during our teleconference call of 10 July 1996, attached please find a summary report of the serious adverse events (SAE) from Population Council Protocol 166A/B that have been reported to the FDA. The tables provide a listing of all subjects who experienced a serious adverse event during the U.S. trial, as well as the location of each reported SAE in the Population Council's IND [redacted]' and NDA 20-687. This summary was generated solely for Council use in preparation for the upcoming July 19 advisory committee meeting. There is no new information in this summary that the agency has not received from us previously in the IND, NDA or NDA safety update--it is just presented in a different format and organization here. However, if you would like me to officially amend our IND and/or NDA with this summary, please inform me of this and I will do so.

I hope this information is helpful for you and other members of your division. Please contact me if you have further questions.

Best regards,

Ann Robbins, Ph.D.
Scientist

cc:S. Arnold

APPEARS THIS WAY
ON ORIGINAL

# MEMO OF TELEPHONE CONVERSATION

3.1

The sponsor was contacted on August 9, 1996, and the following questions were asked:

1) When will their proposed distribution system be submitted? ANS: Expect to send in next week.

2) Do you have an updated draft label? ANS: No waiting for comments from the FDA.

3) Do you have any more (new) post-marketing data from the regulatory agencies in countries in which this drug is approved for marketing (the Britain, Sweden and France)? ANS: No, we have no new data, but have yet to approach regulatory agencies. Please provide names and numbers of regulatory contacts if you have them. The sponsor was told that I would try and obtain this information for them but did not know if I would be successful.

The sponsor was also told that a letter requesting commitments to a variety of Phase IV studies would be sent within a week.

DATE August 9, 1996

NDA/IND NUMBER
NDA 20-687

INITIATED BY

HFD-580

PRODUCT NAME
Mifepristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Robbins, PH.D.

TELEPHONE
(212) 327-8748

FAX

cc:
Orig. NDA

n/

DIVISION HFD-580

The Population Council

Center for
medical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7673
Telephone: (212) 327-8731
Telex: 238274 POBI UR

NEW CORRES

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ORIGINAL

NC

hold
2/19/00

VIA FEDEX

August 15, 1996

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

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

We refer to our above New Drug Application for mifepristone which was submitted on March 14, 1996. As discussed in telephone conversations with 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

Ann Robbins, Ph.D.
Scientist

AR/yho

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 19 1996
HFD-580

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

**The Population Council**

Center for
Biomedical Research

ORIGINAL

1230 York Avenue
New York, New York 10021
Telephone: (212) 327-8748
Facsimile: (212) 327-7678
E-mail: robbins@popcbr.rockefeller.edu

July 25, 1996

ORIG AMENDMENT


Via FedEx

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 ———

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, ———— 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
/S/ 7/29/96
CSO INITIALS DATE

MIF 006530

# The Population Council

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: _____ (letter only, via fax: _____ )

APPEARS THIS WAY
ON ORIGINAL

8.9.8 **Worldwide Safety Information From All Sources**

Serious adverse events were reported in drug surveillance quarterly reports from June 1993 to June 1995.

The listing of all serious adverse events is presented in *Table 6.1.* The protocol number, case identification number, patient age and sex, outcome and causality assessment are listed in this table. A separate listing of serious adverse events where the outcome was reported as death, disabling, not recovered or sequelae is presented in *Table 6.2.* The incidence of these reported serious adverse events is presented in *Table 6.3.* The most frequently reported serious adverse events which were coded were fetal and neonatal adverse events in protocols employing mifepristone in late pregnancy for induction of labor. Copies of all available individual patients records of serious adverse events are presented in *Appendix H (H3).*

Tables 6.1, 6.2, 6.3 attached

Nine patient deaths were reported. Seven of these patients received mifepristone under compassionate use protocols. The patient case numbers are listed in *Table 6.2.* Two of the patients were males, one of these patients was being treated for cushing syndrome (199400320RU) and the other for meningioma (199400138RU). Three female patients were also being treated for meningioma (199500055RU, 199500081RU, and 199500170RU). One female patient was being treated for breast carcinoma (199400250RU) and another for recurrent leiomyosarcoma (199500219RU). A female patient being treated for primary pulmonary hypertension while she awaited heart and lung transplantation died before transplant of progression of disease (199500055RU). The causality of these deaths was assessed as improbable or unlikely to be related to treatment with mifepristone by both the investigator and the sponsor's medical officer. One fetal death that occurred in an ongoing clinical study (FF/91/486/10) is also included in these listings (199400508RU).

Nine patients were reported as having disabling outcomes *(Table 6.2)*. Five of these patients were treated with mifepristone in protocols for induction of labor in late pregnancy (FF/91/486/10). One reported adverse outcome in this study was uterine perforation (199300495RU). Other disabling outcomes reported in this study were axial hypotony (199300480RU), uterine atony (199300484RU), maternal-fetal infection (199400019RU), and fetal distress (199400164RU) A second occurrence of uterine perforation was reported in a patient in protocol FFR/89/486/05 (199400314RU). A case of disabling aphasia was reported in a patient receiving mifepristone for treatment of meningioma (199400389RU). One patient had disabling dyspnea (199400115RU) and one patient had a disabling ovarian cyst (199400114RU). The causality of these events was assessed as unrelated or improbable as to relationship to treatment with mifepristone with the exception of one case of ruptured uterus (199400314RU) and the ovarian cyst patient. These cases were considered to be possibly related to treatment with mifepristone by the investigator and improbably related by the sponsor's medical officer. In this listing an outcome reported as not recovered is interpreted as meaning not recovered at the time the event was reported. Sequelae was interpreted as ongoing treatment at the time of reporting.

Spontaneous notifications of suspected adverse events reported in post-marketing surveillance of mifepristone from June 1989 to June 1995 are presented in *Table 7.*

1st year on market

Table 7 attached

One patient died (MIF/PG0011.91FR) as a result of coronary spasm and myocardial infarction considered unlikely to be related to mifepristone. The coded outcome for one patient with increased transaminase values and jaundice for which there was insufficient data to assess causality was not recovered (MIF/PG0020.92FR). Another patient (MIF/PG0023.93FR) with reported hypotension, galactorrhea and fever considered unlikely to be related to mifepristone was coded as unrecovered for hypotension and fever. All other patients had unknown outcomes or recovered without sequelae.

Worldwide safety information from all sources received during the period of review has been introduced in two safety reports prepared by Roussel. The first, Mifepristone Safety Report (June 1993) covered the period from 01/01/1991 to 12/31/1992. The other, International Safety Report (July 1995), summarizes all the safety data available on mifepristone - whatever the indication - either approved or under investigation, between 01/01/1993 and 05/31/1995. Both reports are available in *Appendix H (H4).*

These are both attached here.

8.9.9 **Animal Data**

Mifepristone proved to have little if any toxicity in a single dose of 100 mg/kg in the mouse, rat or dog. Treatment lasting 1 month or 6 months in the rat and monkey revealed no genuine toxicity. The observed effects found expression in the form of biochemical variations and modifications in body weight and histopathological findings in the organs targeted by the antiglucocorticoid, antiprogestrone and anti-androgenic activities of mifepristone. The monkey, in this case, proved more sensitive than the rat to these endocrine disorders. In view of the proposed treatment conditions whereby mifepristone is to be administered in a single dose only, long-term studies in animals were not considered appropriate.

In conclusion, mifepristone is a product which has little toxicity and which in these studies clearly demonstrates the antihormonal properties revealed by pharmacological research. To this expected combination of effects, enhanced by the treatment design inherent in toxicology studies, should be added a probable indirect activity by mifepristone on the foetus in the rabbit but not in the rat and mouse. By way of precaution, in women this will necessitate the implementation of the appropriate steps to ensure the therapeutic purpose is fully achieved.

8.9.10 **Analysis of Adverse Effect Dose-Response Information**

Since all patients in the pivital trials received the same dose of mifepristone, no information is available on the effect of dose in the incidence of adverse events.

8.9.11 **Drug-Drug Interactions**

There is no information on drug-drug interactions available from these clinical trials.

8.9.12 **Drug-Demographic and Drug Disease Interactions**

The probability of occurrence of the principal adverse effects of treatment with mifepristone in combination with misoprostol is related to certain demographic characteristics of the population which was treated. These probabilities were calculated using a stepwise logistic regression analysis. The probability of painful contractions of the uterus decreased with increasing patient age up to 33 years *(Figure 1)* and decreased with increasing numbers of prior pregnancies up to 4 previous pregnancies *(Figure 2)*.

The probability of occurrence of nausea and vomiting after treatment increased at higher gestational ages *(Figure 4)* and increased in patients with more prior abortions *(Figure 5)*. The probability of occurrence of nausea and vomiting decreased with increased number of prior pregnancies *(Figure 6)*. The probability of occurrence of diarrhea increased with increasing patient age *(Figure 7)* and decreased with the number of prior pregnancies *(Figure 8)*.

The probability of hemoglobin decreases of at least 20% following treatment increased in patients with gestational ages up to 49 days and decreased at gestational ages above about 50 days.

8.9.13 **Pharmacologic Properties Other Than the Property of Principal Interest**

Mifepristone has antiglucocorticoid activity which, in animal studies, is manifest at higher dose than required to obtain antiprogestin activity. The antiglucocorticoid activity of mifepristone has not been extensively studied in humans (*see Clinical Pharmacology, Section 8.3*).

8.9.14 **Long Term Adverse Effects**

In studies of mifepristone for termination of first trimester pregnancy, only one dose of mifepristone is administered. The long term effects of this single dose have not been studied.

8.9.15 **Reference List** - *Reports located in NDA Volumes as indicated in the table that follows.*

Population Council

ORIGINAL

This is not the complete original 10/2/97

**Sandra P. Arnold**
Vice President
Corporate Affairs

ORIG AMENDMENT
BC

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

September 24, 1997

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

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 009 - Chemistry, Manufacturing and Controls**

Dear

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: [redacted]
Advances/The NeoGen Group

[redacted]

Dr. Ann Robbins
The Population Council

Dr. Frederick Schmidt
The Population Council

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Population Council

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

noted 11/26/97 /S/

ORIG AMENDMENT

November 26, 1997

———

——— 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 /S/ DATE

**RE: NDA 20-687, Mifepristone 200 mg Oral Tablets**
**Amendment 010 - Revised Physician Labeling**

Dear ———

Enclosed please find our suggested additions to the proposed mifepristone label currently being considered by the Food and Drug Administration (FDA). These additions incorporate the data from the U.S. trials, as has been requested by the FDA. In addition to the description of the additions, a copy of the document is provided on diskette.

Thank you for your assistance in this matter.

Best regards,

Charlotte Ellertson

Charlotte Ellertson, M.P.A., Ph.D.
Program Associate

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | November 26, 1997 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0607 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052 |

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

1230 York Avenue
New York, NY 10021

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

## PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)* RU 486

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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

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

CERTIFICATION

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

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

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Charlotte Ellertson KB | Charlotte Ellertson, Program Associate | 11/26/97 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| One Dag Hammarskjold Plaza, New York, NY 10017 | (212) 339-0607 |

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

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**FORM FDA 356h (7/97)**



MIF 006540

ORIGINAL

ORIG AMENDMENT

# The Danco Group

May 10, 1999

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


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

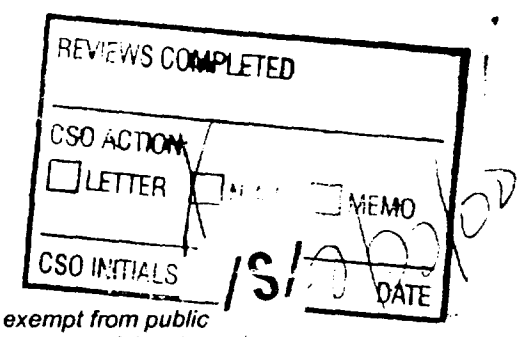
**Re: NDA 20-687, Mifepristone 200mg Oral Tablets**

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

Dear

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




*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 :*

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/

[redacted]

President and
Chief Executive Officer

/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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | May 10, 1999 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710 |

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

1230 York Avenue
New York, NY 10021

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

## PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*

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

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

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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



MIF 006543

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
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| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
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| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Information on Manufacturer of Drug Substance |

CERTIFICATION

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

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5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Sandra P. Arnold | Sandra P. Arnold, Vice President | 05/10/99 |

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

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**FORM FDA 356h (7/97)**

# The Danco Group

ORIGINAL

NEW CORRESP

April 28, 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 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 [redacted] 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,

[redacted]

President and
Chief Executive Officer

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

REVIEWS COMPLETED
[redacted]
CDD ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
[redacted] /S/ DATE

MIF 006545

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | April 28, 1999 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1230 York Avenue<br>New York, NY 10021 | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

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

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (Chemical Abstracts) - (11β,17β)-11-[(4-Dimethylaminophenyl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

CODE NAME *(If any)*

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

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

## APPLICATION INFORMATION

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REASON FOR SUBMISSION

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| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Scheduling of Preapproval Inspection Audit |

CERTIFICATION

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
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| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Frederick H. Schmidt for | Sandra P. Arnold, Vice President | 04/28/99 |

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

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**FORM FDA 356h (7/97)**

**Examples of Trade Names with Initial Letters Identical to Generic Name**

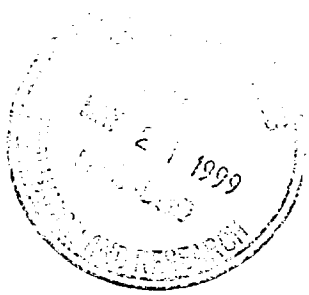
| Generic Name | Trade Name | Company |
|---|---|---|
| AMOXICILLIN | AMOXIL | SKB |
| BECLOMETHASONE | BECLOVENT | Glaxo-Wellcome |
| CIPROFLOXACIN | CIPRO | Bayer |
| COLESTIPOL | COLESTID | Pharm & Upjohn |
| DESOGESTREL | DESOGEN | Organon |
| DOBUTAMINE | DOBUTREX | Lilly |
| ERYTHROMYCIN | ERYTHROCIN | Abbot |
| FELBAMATE | FELBATOL | Wallace |
| GUAIFENESIN | GUAIFED | Muro |
| MEPERIDINE | MEPERGAN | Wyeth-Ayerst |
| MINOCYCLINE | MINOCIN | Lederle |
| MIVACURIUM | MIVACRON | Glaxo |
| NAFTIFINE | NAFTIN | Allergen |
| NAPROXEN | NAPROSYN | Roche |
| PANCRELIPASE | PANCREASE | Ortho |
| QUINIDINE | QUINIDEX | Robins |
| RIFAMPIN | RIFAMATE | HMR |
| RISPERIDONE | RISPERDAL | Jenssen |
| SUFENTANIL | SUFENTA | Taylor |
| TICARCILLIN | TICAR | SKB |
| TOBRAMYCIN | TOBRADEX | Allon |
| VANCOMYCIN | VANCOCIN | Lilly |

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

/S/ 5/27/99

**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 /S/ 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. [redacted] had recently indicated that they required this action before the drug substance could be shipped by Danco to the site.

Please let me know if you require any additional information.

Sincerely,

[redacted]

[redacted]

President and
Chief Executive Officer

/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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | May 20, 1999 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1230 York Avenue<br>New York, NY 10021 | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

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

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

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

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

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

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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

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

CERTIFICATION

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

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

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Frederick A. Schott for | Sandra P. Arnold, Vice President | 05/20/99 |

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

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

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Please **DO NOT RETURN** this form to this address.

**FORM FDA 356h (7/97)**



MIF 006552

6-1

# Meeting Minutes

**Date:** April 9, 1999 **Time:** 10:00 AM - 11:30 AM **Location:** Parklawn C/R 17B-43

**NDA** 20-687 **Drug Name:** mifepristone tablets

**External Participant:** The Population Council

**Type of Meeting:** CMC status update

**Meeting Chair:** [redacted]

**External Participant Lead:** [redacted]

**Meeting Recorder:** [redacted]

**FDA Attendees:**

[redacted] Division of Reproductive and Urologic Drug Products

[redacted] DRUDP (HFD-580)
[redacted], Office of New Drug Chemistry
[redacted], Division of New Drug Chemistry II
(DNDC II) @ DRUDP (HFD-580)
[redacted], Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)
[redacted] DRUDP (HFD-580)
[redacted]

**External Constituents:**
**Population Council**
Ms. Sandra Arnold - Vice-President

**Danco Laboratories/The NeoGen Group**
[redacted]

**Meeting Objectives:**
To discuss the current status of chemistry, manufacturing and controls (CMC) development by the sponsor and anticipated dates for submission of a complete response to the approvable letter issued on September 18, 1996

**Discussion Points:**

- Drug Substance
  - the drug substance is manufactured at a Chinese site
  - [redacted] validation batches ([redacted]) were placed on stability earlier this year
  - according to the sponsor, the drug substance has been tested and meets all of the Rousell Uclaf (RU) specifications

**Unresolved Issues:** none

**Action Items:** see decisions reached

/S/
Minutes Preparer 4/20/99

/S/
Concurrence, Chair

cc:
Orig.
HFD-580
MEETING ATTENDEES

4.19.99

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NEW CORRESP

NC

# The Danco Group

/S/ 4/6/99 noted 4/6/99 /S/

not sup /S/ 4/5/99

March 31, 1999

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

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

Dear ———

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 ——— 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 United States.

A. Facility

REVIEWS COMPLETED

CSO ACTION:

☐ LE☐ ☐ N.A. ☐ MEMO

/S/

MIF 006555

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 - [redacted] – President and Chief Executive Officer
- [redacted]
- [redacted]
- [redacted]

Sincerely.

[redacted]

[redacted]

President and Chief Executive Officer

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

APPEARS THIS WAY
ON ORIGINAL

**EXHIBIT 1**

**Danco Laboratories, Inc.**

**Timetable for Drug Substance and Drug Product Production and FDA Submissions**

1. Early January 1999 - Drug Substance —— validation batches produced and tested
2. March 1999 - Drug Substance Samples tested in ———— FDA-approved testing site
3. Early May 1999 - Drug Substance CMC submission with 3 months accelerated stability
4. Early May - Drug Product facility will run demonstration batch
5. End May - Drug Product CMC ready for submission (no stability data)
6. Early June - Submit Drug Product CMC with 1 month's accelerated stability
7. June/ July - Drug Substance site ready for PAI
8. June/ July - Drug Product site ready for PAI
9. August - Submit 3 months accelerated stability for Drug Product and 6 months accelerated stability for Drug Substance
10. November - Submit 6 months accelerated stability for Drug Product and 9 months accelerated stability for Drug Substance

APPEARS THIS WAY
ON ORIGINAL

Exhibit 2

# Memo

To: [redacted]

From: [redacted] VS

Date: April 1, 1999

Re: [redacted]

We retained [redacted] to work with both of our foreign substance manufacturers in order to assist bringing them into compliance with the US FDA's cGMPs guidelines.

We chose [redacted] because of his reputation and experience specifically in both countries involved on an ongoing basis for over 10 years. His record of success is impressive having participated in over a dozen audits there; the FDA has approved all of them. His most recent approvals occurred in early 1999.

APPEARS THIS WAY
ON ORIGINAL

# memorandum

**Date:** March 31, 1999

**Company:** Danco Investors Group, L.P.

**Attention:** [redacted] President & Chief Executive Officer

**From:** [redacted]

**Re:** Compliance Status Update APPEARS THIS WAY ON ORIGINAL

Since becoming involved with the [redacted] in April '98, I have audited their plant on five different occasions. Following the January '99 audit and subsequent correspondence with their staff on related matters, I would like to summarize their current compliance status as follows:

- *Facilities*: The facilities have been upgraded and modified to accommodate the process provided by Danco.

- *Process*: Following a technology transfer protocol, the company's staff was successful in consistently producing Mifepristone following the modified process at the laboratory level ([redacted] lots).

  Subsequently, the process was scaled up and [redacted] lots of Mifepristone have been produced at the plant level ([redacted] scale).

  The production of these [redacted] lots was covered by an adequate validation protocol. The pertaining report establishes the consistency required to assert that the process is validated.

- *Quality Control*: The Quality Control Laboratory has been audited during our visits to the firm and it is now fully equipped to test raw materials, intermediates and final product. The general facilities have also been improved in order to meet adequate levels of GLP compliance.

- *Quality Assurance*: The Quality Assurance group, in conjunction with all other departments, has been actively involved in the preparation of an extensive list of Operating Procedures, Validation Protocols, Installation and Operation Qualification Protocols and related reports. For our benefit, most of these have been translated into English and the final versions are acceptable.

# memorandum

Danco Investors Group, L.P.
March 31, 1999

- *FDA Submission (CMC Section)*: This document is currently under preparation following our guidance, and a final draft is expected to be available for our review April 15, 1999.

Taking the above synopsis under consideration, we expect to audit the
one more time (*early June*) and it is our opinion that the company should be ready for pre-approval inspection in July of this year.



15 Engle Street, Suite 103, Englewood, New Jersey 07631-2920 U.S.A. Tel. (201) 816-5535 Fax (201) 816-5538

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | April 1, 1999 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710 |

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

1230 York Avenue
New York, NY 10021

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

## PRODUCT DESCRIPTION

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

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

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

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

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

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

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



MIF 006562

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
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| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Product and Submission Timetable for FDA Meeting on 4/9/99 |

CERTIFICATION

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

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3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
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7. Local, state and Federal environmental impact laws.

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| for Richard A. Scott | Sandra P. Arnold, Vice President | April 1, 1999 |

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

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

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

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

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)



MIF 006563

ORIGINAL

# The Danco Group

February 22, 1999

BC
Received. This is not a complete response to the 1/27/99 FDA letter. I will review when the sponsor has responded completely to the Biometrics comments in that letter


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

Dear

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.

1.

2.

3.

5. [redacted]

6. Point #6 – We understood from the teleconference that the FDA has changed its position and is now initially looking for the in-process impurities specification for [redacted] We will not make any changes in this specification until we have collected the appropriate data from our new [redacted] of bulk mifepristone and reviewed with the FDA.

7. Point #7 –As agreed during the teleconference, the drug specification for [redacted]

8. Point #8 – This will be provided when we have collected the data from our new manufacturers.

9. [redacted]

11 [redacted]

use.

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 ☐ MEMO
INITIALS 4/3/99

Sincerely,

/S/

President and
Chief Executive Officer

CC:
Sandra P. Arnold – Population Council

[redacted]

ORIGINAL

Population Council

**Sandra P. Arnold**
Vice President
Corporate Affairs

NEW CORRESP

12/21/98

1/26/99

CENTER FOR DRUG
REC'D
DEC -9 1998
HFD-580
EVALUATION AND RESEARCH

noted
12/20/98

December 8, 1998

VIA FEDERAL EXPRESS

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

Thank you very much for the minutes of the meeting held at your offices on November 2, 1998. I have reviewed them with , 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 's name to end in
- Please add of the firm of

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 ms of bulk drug substance, pending resolution of manufacturing issues."

- Discussion of Dose Changes - mifepristone and misoprostol

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

We would also appreciate it if you would change the final bullet to read: "the sponsor has not yet made a final decision [redacted]

Decisions Reached
We believe that in the second bullet the term [redacted] " 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 [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,

[redacted]

cc: [redacted]

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

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☒ N.A.I. ☐ 10
CSO INITIALS 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | December 8, 1998 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 980-3710 |

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

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

## PRODUCT DESCRIPTION

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

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

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)* |
|---|---|
| | RU 486 |

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
| | B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| | C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2) |
| | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
| | 9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2) |
| | 10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2) |
| | 11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) |
| | 12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Correspondence Regarding Changes in Minutes of Nov. 2, 1998 Meeting. |

CERTIFICATION

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

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

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Sandra Arnold | Sandra P. Arnold, Vice President | 12/8/98 |

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

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

DHHS, Reports Clearance Officer
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FORM FDA 356h (7/97)

ORIGINAL

NEW CORRECTED

# The Danco Group

noted. response to Sponsor during 2/16/99 T-con. 2/23/99


February 8, 1999

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**

Dear

This letter is in response to D.'s 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:

1. Point #2 - you are referring to relate to a specific reference in the submission? If so, please give the page reference.

2. Point #4 - Is the FDA's concern that this test was not listed in the which could have been a clerical error?

3. Point #6 - The recommendation that the or

4. Point #7 - The recommendation that the

The data on the batches made by Gedeon Richter show that

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

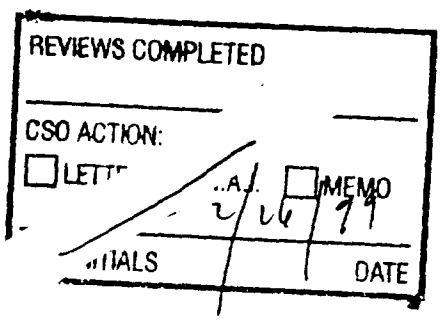
Sincerely,

/s/

President and
Chief Executive Officer

Cc:
Sandra P. Arnold – Population Council

APPEARS THIS WAY
ON ORIGINAL



# Meeting Minutes

**Date**: November 2, 1998 **Time**: 2:00 PM - 3:30 PM **Location**: Parklawn C/R 17B-43

**NDA** 20-687 **Drug Name**: mifepristone

**External Participant**: The Population Council

**Type of Meeting**: CMC guidance

**Meeting Chair**:

**External Participant Lead**: Sandra Arnold

**Meeting Recorder**:

**FDA Attendees**:
, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
- Chemist, DNDCII @ DRUDP (HFD-580)

**External Constituents**:
**Population Council**
Ms. Sandra Arnold - Vice-President
Patricia C. Vaughn, Esq. - Legal Councel
*Frederick Schmidt, Ph.D. - Scientist*

**Danco Laboratories/The NeoGen Group**
, President
Manufacturing Consultant

**Meeting Objectives**:
To discuss the sponsor's CMC plans and the deficiencies identified in the partial response submitted September 1997.

**Discussion Points**:

- Status Report - Sponsor Presentation

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

  - the first three validation batches of tablets are expected to be submitted to the Division in March 1999

- Response to approvable letter and Stability

  - the sponsor plans to submit portions of the CMC response as they become available
  - the sponsor must submit a complete response to the deficiencies detailed in the approvable letter before the user fee clock can be started; the sponsor must also declare that they have submitted all required information once the last piece of information is submitted
  - the sponsor must submit stability data from the current manufactures, they may not rely on stability data generated by former manufacturers of the drug product or drug substance
  - current ICH requirements for stability are 6 months accelerated and 12 months real time data to consider a 2 year expiration date

- September 1997 partial response

  - [redacted]

[redacted]

[redacted]

- Manufacture of bulk drug substance

  - drug substance will be manufactured according to Rousell Uclaf's method
  - the starting material will be [redacted]
  - [redacted] can be obtained both in Europe and China, the manufacturer will obtain their supply from China
  - data on multiple batches of the starting material should be submitted in order to ensure that there is consistency between batches

- the drug substance manufacturers will ensure that all specifications of their product are in agreement with those of RU (i.e.,
- the manufacturers should provide of their drug substances to identify and quantify their impurity profile
- the biggest change between the RU method and method to be utilized are changes in which are not expected to cause any difference in drug substance profile
- the manufacturer must be able to demonstrate that the tablets manufactured are equivalent to those made by RU, guidelines for these *in vitro* tests are found in the SUPAC guidance document
- bioequivalence testing may also be required, however, this can not be determined until comparative dissolution data has been submitted
- the sponsor requests that inspections be scheduled as soon as the manufacturers are ready for inspection

- Discussion of Dose Changes - mifepristone and misoprostol
  - investigators here and clinicians in Europe are utilizing mifepristone
  - the Population Council currently has data from 4 clinical studies (2 completed, 2 nearing completion) for the 200 mg mifepristone dose
  - the sponsor claims no statistical difference in efficacy between the two doses
  - all four clinical studies utilized mg oral administration (oral misoprostol was used in studies submitted in the NDA)
  - a bridging study will be prepared to demonstrate equivalence between the vaginal and oral route of administration
  - the sponsor intends to submit this clinical data along with the CMC data to their NDA to support the use of a lower dose of mifepristone
  - the sponsor would also like to pursue the home administration of misoprostol instead of clinic administration studied in the original clinical trials
  -

**Decisions Reached**:

- the manufacturing plan for the bulk drug substance appears acceptable
- a complete response to the deficiency letter should include sufficient stability data to support the expiration date the sponsor intends to request
- although the Division is under no obligation to review a partial submission to an approvable letter, the Chemistry reviewer will attempt to complete the review of the September 1997 partial response submission by the end of December 1998. A detailed letter of deficiencies noted in the review will be issued based upon that review
- manufacturing site inspections can be requested before a complete response is submitted, however timing of inspections cannot be guaranteed. The sponsor should provide location and contact numbers for the inspections once they are ready to have the sites inspected

- it is unclear at this time if the sponsor can change the clinical parameters for the current NDA, the Division will discuss this request with the Office Director. The sponsor may be required to submit another NDA for these clinical changes

**Unresolved Issues**: how to submit clinical changes to the current NDA application

**Action Items**:

| Item | person responsible | time frame |
|---|---|---|
| 1. Completion of CMC partial resp. Review | [redacted] | Possibly by 1/99 |
| 2. Issue deficiency letter based on (1) | | 2 wks after review |
| 3. Report results of clin. data change discussion | | 2 weeks |

/S/ 11/19/98
Minutes Preparer

/S/
Concurrence, Chair

**Post-meeting note**: [redacted] spoke with the [redacted] regarding submission of new clinical data. The sponsor may submit the clinical data as a new NDA (referring to NDA 20-874 for non-clinical information) or they may submit the CMC data required for approval of the existing NDA, receive approval for that NDA and then submit the clinical data as an efficacy supplement to the approved NDA. The sponsor was informed of this decision by [redacted] in a telephone conversation on November 5, 1998.

cc:
Orig. IND
HFD-580
MEETING ATTENDEES

[redacted]

9.98

MEETING MINUTES

Population Council

NC

NEW CORRESP

**Sandra P. Arnold**
Vice President
Corporate Affairs

/S/ 11/4/98

October 26, 1998

VIA FEDERAL EXPRESS


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

/S/ 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

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?

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

III. Discussion by one of the two 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. Discussion of the use of —— mifepristone versus the 600 mg in the NDA. Specific questions are:

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

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 —— 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 two 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.

[ ]

Very truly yours,

for Andrea Arnold

cc:

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

**APPEARS THIS WAY ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | 10/26/98 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*: RU 486

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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



MIF 006579

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | 10/26/98 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)* RU 486

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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



MIF 006580

This application contains the following items: *(Check all that apply)*

| | |
|---|---|
| | 1. Index |
| | 2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling |
| | 3. Summary (21 CFR 314.50 (c)) |
| | 4. Chemistry section |
| | A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) |
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| | 5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2) |
| | 6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2) |
| | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
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| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A)) |
| | 15. Establishment description (21 CFR Part 600, if applicable) |
| | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| | 17. Field copy certification (21 CFR 314.50 (k) (3)) |
| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Agenda for FDA Meeting on November 2, 1998. |

CERTIFICATION

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

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

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

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| /s/ for SANDRA ARNOLD | Sandra P. Arnold, Vice President | 10/26/98 |

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

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Paperwork Reduction Project (0910-0338)
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200 Independence Avenue, S.W.
Washington, DC 20201

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**FORM FDA 356h (7/97)**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | June 26, 1998 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052 |

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

1230 York Avenue
New York, NY 10021

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

## PRODUCT DESCRIPTION

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

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY | CODE NAME *(If any)* |
|---|---|---|
| Mifepristone | Not available | RU 486 |

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

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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

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

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

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

REASON FOR SUBMISSION

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

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

## ESTABLISHMENT INFORMATION

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

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



MIF 006582

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

CERTIFICATION

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

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5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Sandra P Arnold ws | Sandra P. Arnold, Vice President | 06/26/98 |

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

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

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**FORM FDA 356h (7/97)**

ORIGINAL

**Population Council**

**Sandra P. Arnold**
Vice President
Corporate Affairs

/S/ 5/7/98

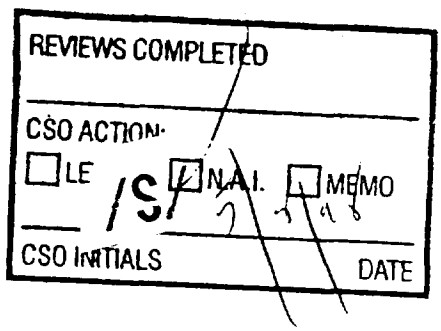
/S/ 5/4/98

/S/ 5/8/98


April 27, 1998

Transmitted via Federal Express

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

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 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, was not in attendance and should be deleted from the list of attendees. Additionally, should be listed as, 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

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

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,

[redacted]

cc: [redacted]
[redacted]
[redacted]).
Frederick Schmidt, Ph.D.
Patricia C. Vaughan, Esq.

APPEARS THIS WAY
ON ORIGINAL

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Population Council | April 27, 1998 |
| **TELEPHONE NO.** *(Include Area Code)* (212) 339-0663 | **FACSIMILE (FAX) Number** *(Include Area Code)* (212) 755-6052 |

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

1230 York Avenue
New York, NY 10021

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## PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)* RU 486

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

(PROPOSED) INDICATION(S) FOR USE:

Induction of abortion

## APPLICATION INFORMATION

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Name of Drug — Holder of Approved Application

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REASON FOR SUBMISSION

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

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| | 7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) |
| | 8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) |
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| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A)) |
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| | 18. User Fee Cover Sheet (Form FDA 3397) |
| X | 19. OTHER (Specify) Correspondence regarding minutes of March 16, 1998 meeti |

CERTIFICATION

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
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| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Sandra Arnold | Sandra P. Arnold, Vice President | 4/27/98 |

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

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Washington, DC 20201

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FORM FDA 356h (7/97)

# Meeting Minutes

**Date**: March 16, 1998 **Time**: 2:00 PM - 3:30 PM **Location**: Parklawn 17B-43

**NDA** 20-687 **Drug Name**: mifepristone tablets

**External Participant**: The Population Council

**Type of Meeting**: Regulatory Guidance

**Meeting Chair**: [redacted]

**External Participant Lead**: Ms. Sandra Arnold

**Meeting Recorder**: [redacted]

**FDA Attendees**:

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

[redacted], Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

[redacted].- Chemist, DNDCII @ DRUDP (HFD-580)

[redacted], Office of New Drug Chemistry (ONDC; HFD-800)

[redacted]. - Medical Officer (HFD-580)

**External Constituents**:

**Population Council**

Ms. Sandra Arnold - Vice-President

Patricia C. Vaughn, Esq. - Legal Councel

Frederick Schmidt, Ph.D. - Scientist

**Danco Laboratories/[redacted]**

[redacted]

**Meeting Objectives**:

To discuss a proposal for responding to the Chemistry, Manufacturing, and Controls (CMC) issues delineated in the Approvable (AE) letter dated September 18, 1996.

**scussion Points**:

- CMC update
  - two potential manufacturers ('A' & 'B') of bulk drug substance have been identified
  - a meeting request will be submitted for a CMC discussion with manufacturer 'A' in May

- manufacturer 'A' will initiate small scale production in their — laboratory to ensure process and product consistency
- commercialized batches will be produced in an off-shore manufacturing facility owned by manufacturer 'A'
- the sponsor requests the Division schedule inspections for the fourth quarter of 1998 although they do not expect a complete CMC response to the AE letter before the first quarter of 1999
- tableting will be performed by a different manufacturer also in an off-shore facility

- Reference Standards

  - the sponsor intends to demonstrate comparability of Roussel Uclaf (RU) bulk drug substance and Gedeon Richter (GR) bulk drug substance
  - the sponsor intends to use the GR specifications as the reference for future manufacture of the drug substance
  - information regarding both GR and RU's bulk drug substance was submitted in September 1997
  - although the September submission is not a complete response to our approvable letter the Division has agreed to review the information pertaining to equivalency of standards by the end of May
  - although review of the September submission is not complete, several deficiencies have already been identified; some of these relate to the demonstration equivalence between GR and RU's drug substance lots
  - upon completion of the review those deficiencies and any others identified with regard to equivalency will be provided in a detailed information request letter
  - minor changes in process between RU and GR may be acceptable
  - the sponsor is reminded that the AE letter requested some RU specifications be tightened
  -

- Compassionate Use

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- Additional Dosage Information

- the sponsor is concerned that with a labeled dose of [redacted] s) for their product, physicians may use only one tablet
- should this occur, the proposed distribution controls may not be effective
- this situation is currently the case in Great Britain
- the sponsor requests guidance regarding amending their dosage and administration instructions with this new information

- **Decisions Reached**

  - the Division will review the September CMC submission with respect to equivalency of bulk drug substance issues
  - upon completion of that review a detailed letter of deficiencies will be issued
  - conceptually, it may be acceptable for a manufacturer to have a starting material [redacted] well characterized to ensure appropriate
  - manufacturing site inspections are not normally granted until a complete response is submitted
  - the Division will consult with the Office of Drug Evaluation II and others regarding an early site inspection
  - if the sponsor can demonstrate equivalence between the RU and GR bulk drug substances, they may tablet the substance and issue for compassionate use provided there is no change in composition or components of the tablets and the sponsor can demonstrate equivalence of tablet dissolution with the RU tablets
  - the sponsor has three routes to make a change in dosage; they may:
    - obtain right of reference to both the clinical and CMC data from the IND investigator and submit that to the Division for consideration
    - obtain information from a literature search of clinical trials in which this alternative dosage is described and submit that to the Division for consideration
    - perform their own clinical trials
    - if relying on trials performed by other investigators, the sponsor must show equivalency of drug product used in those trials

**Unresolved Issues**: none

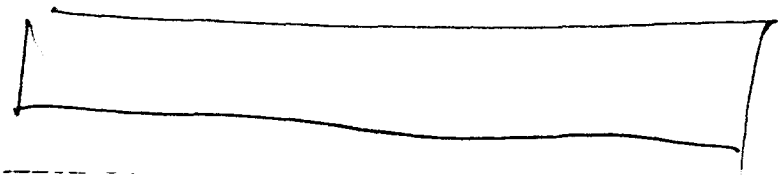
**Action Items**: see Decisions Reached

/S/ 3/23/98
Minutes Preparer

/S/
Concurrence, Chair

ATTACHMENT
sponsor overheads

cc:
Orig. NDA
HFD-580
MEETING ATTENDEES



APPEARS THIS WAY
ON ORIGINAL

# Mifepristone
## Meeting Objectives

- Provide Background on NeoGen and Mifepristone
- Review bulk substance & tableting manufacturing/regulatory strategy
- Obtain Agreement to use Roussel substance and tablets as "reference standards"
- Determine FDA acceptance of Gedeon Richter substance as additional "reference standard" based on filed CMC.

Other

- Compassionate use of Gedeon Richter substance
- 200mg dosage

# The NeoGen Group
## General

- Partnership with individual investors
- General Partners control business
- Key Personnel
  - [redacted] - President & Chief Operating Officer
  - [redacted] - Vice President Manufacturing
  - Heather O'Neill - Director Public Affairs
  - [redacted] - Controller
- Major Asset: Mifepristone US
  - Potential rights in other countries
- Located in New York City

# The NeoGen Group
## Corporate Goals

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# Mifepristone
## Abbreviated Regulatory History

| | |
|---|---|
| April 1983 | First IND on medical abortion |
| Aug. 1994 | First IND for US trials |
| March 1996 | NDA filed |
| July 1996 | FDA Advisory Committee |
| Sept. 1996 | Approvable Letter<br>- Subject to manufacturing & other issues |
| Aug./Sept. 1997 | Amendments on CMC from Gedeon Richter |
| November 1997 | Revised labeling to include US trial data |

# Mifepristone
## Bulk Substance/Regulatory Strategy

### Manufacturer A (Agreement in Place):

- **Laboratory work in USA at well-known facility**
  - Make batches consistent with Roussel chemistry
  - Define Process
  - Prepare technology transfer document
- **Begin pilot batch/scale up in off-shore factory**
  - Produce [redacted] validation batches
  - Finalize SOP's, training and cGMP upgrade program
  - Prepare CMC section and file

# Mifepristone
## Bulk Substance/Regulatory Strategy

**Manufacturer (cont'd):**

- Plant inspection by FDA in 4Q98
- Produce ——— validation batches for commercial use
  - File supplement

- Timeframe: File CMC section ———) in 4Q98

# Mifepristone
## Bulk Substance/Regulatory Strategy

**Manufacturer | :**

- **Same as Manufacturer A except laboratory work completed and factory currently produces Mifepristone (no pilot necessary - producing [redacted] batches)**

- **Timeframe: File CMC section in 4Q98**

# Mifepristone
## Tableting/Regulatory Strategy

- **Status**
  - Reviewing factory options
  - Close to one - currently upgrading
- **Tablet validation batches from substance validation batches**
  - 3 months accelerated stability
- **Plant inspection by FDA in 1Q99**
- **Timeframe: File CMC Section in 1Q99**

# Mifepristone
## Summary of Regulatory Strategy

- File validation batches of substance
- Supplement for commercial batch sizes
- Utilize Gedeon Richter or Roussel as bulk substance "reference standard"
- File tablet validation batches with 3 months accelerated stability
- Utilize Roussel tablets as "reference standard"

# Mifepristone
## GR Process Differences

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