The Population Council

Center for
Biomedical Research

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

VIA FEDEX

September 16, 1996

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

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

Dear ———

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

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

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

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

Sincerely,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yho

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
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Telex: 238274 POBI UR

ORIGINAL

December 7, 1994

Mailed
12/14/94
/S/

BY FEDEX

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

Subject: IND —— Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

NDA
/S/
16 Dec 94

Dear ——

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to —— of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

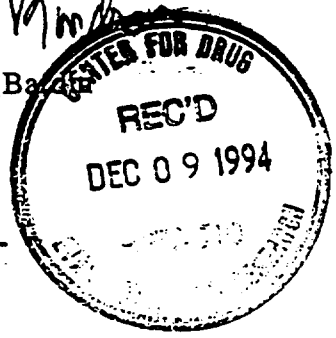
Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Bardin

C. Wayne Bardin



REVIEWS COMPLETED

CSO ACTION:

☐ [illegible] ☐ N.A.I.

/S/ 12/16/94

CSO INITIALS / DATE

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014. Expiration Date: November 30, 1995. See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
The Population Council

2. DATE OF SUBMISSION
December 07, 1994

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 327-8717

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Mifepristone Tablets

6. IND NUMBER *(If previously assigned)*
IND ——

7. INDICATION(S) *(Covered by this submission)*
Induction of abortion

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 109

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☒ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION

☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW: REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (12/92) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

MIF 001604

12. CONTENTS OF APPLICATION

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

- ☐ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED Please refer to Submission 100

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

C. Wayne Bardin, MD
Vice President and Director
The Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

C. Wayne Bardin, MD
Vice President and Director
The Population Council

Irving M. Spitz, MD
Senior Scientist
The Population Council

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
C. Wayne Bardin, MD	C. Wayne Bardin	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1230 York Avenue New York, NY 10021	(212) 327-8717	12/07/94

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 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:

Reports Clearance Officer, PHS
Humbert H. Humphrey Building, Room 721-H
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

The Population Council
Center for
Biomedical Research

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

ORIGINAL

52

November 21, 1994

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

Subject: IND ——— - Mifepristone Tablets, 200 mg
Submission Serial #107
IND Safety Report

Dear ———

Please find enclosed a copy of FDA Form 3500 in reference to the adverse event reported to you on November 18, 1994 by Dr. Irving Spitz of the Population Council in the above referenced study. In addition, we have enclosed a copy of the text prepared by the physician at the site where the adverse event occurred.

If you require any additional information please contact me.

Sincerely,

C.W. Bardin

C. Wayne Bardin, M.D.
Director

CENTER FOR DRUGS
REC'D
NOV 23 1994
HFD-510
EVALUATION AND RESEARCH

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I.
/S/ 11/1/94
CSO INITIALS DATE

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014. Expiration Date: November 30, 1995. See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
The Population Council

2. DATE OF SUBMISSION
November 21, 1994

3. ADDRESS (Number, Street, City, State and Zip Code)
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER (Include Area Code)
(212) 327-8731

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)
Mifepristone Tablets

6. IND NUMBER (If previously assigned)
IND —

7. INDICATION(S) (Covered by this submission)
Induction of abortion

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ (Specify)

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SERIAL NUMBER: 107

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☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

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CHECK ONLY IF APPLICABLE

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☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/OBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D NOV 23 1994 HFD-510

FORM FDA 1571 (12/92) PREVIOUS EDITION OBSOLETE

MIF 001607

CONTENTS OF APPLICATION

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

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- ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
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] 10. Additional information *[21 CFR 312.23 (a) (10)]*

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IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED Please refer to Submission 100

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C. Wayne Bardin, MD
Vice President and Director
The Population Council

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C. Wayne Bardin, MD
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C. Wayne Bardin, MD	C Wayne Bardin	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1230 York Avenue New York, NY 10021	(212) 327-8717	11/21/94

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

FORM FDA 1571 (12/92)

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): 13

Send to Facsimile Number: ———

Date: 14 July 1996

Send to Company: FDA,
Division of Reproductive
and Urologic Drug Products

Send to Person: ———

Subject: U.S. Safety Data

Dear ——

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 —— 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

APPEARS THIS WAY
ON ORIGINAL

cc:S. Arnold

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 IND [redacted] 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
23				
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 IND

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
( )	22	Hemorrhage	X		X	X	X	63		107 11/21/94
	02	Hemorrhage Vomiting Fainting	X		X			44		108 12/01/94
	02	Vomiting Diarrhea Dehydration			X			49		108 12/01/94
	02	Hemorrhage Cramping	X			X	X	53	East Asian	109 12/07/94
	02	Hemorrhage Cramping Dizziness	X		X		X	51	Cau-casian	109 12/07/94
	01	Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia	X		X	X		44		110 12/20/94
	25	Hemorrhage Cramping	X+					46		113 01/18/95
	25	Hemorrhage Cramping	X					49		113 01/18/95
	01	Hemorrhage Weak Nausea Pale & Cold			X			57		113 01/18/95
	02	Hemorrhage Vomiting Cramping Chlamydial infection								113 01/18/95
	03	Hemorrhage Syncope Pallor	X	X				52		113 01/18/95
	25	Hemorrhage Cramping Feeling Faint	X		X		X	56		114 01/23/95
	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
	26	Hemorrhage Cramping Syncope	X		X		X	57		115 02/07/95
	01	Hemorrhage Cramping	X				X	57	His-panic	118 02/15/95
	01	Vomiting Dizziness			X					118 02/15/95
	01	Hemorrhage	X	X			X	62	His-panic	118 02/15/95
	01	Hemorrhage Dizziness Headache		X	X			53		118 02/15/95
	04	Hemorrhage	X		X			65		118 02/15/95
	01	Hemorrhage Fever	X		X		X	45		119 02/17/95
	01	Chest Pain					X			119 02/17/95
	03	Hemorrhage Tachycardia	X				X	51		120 03/03/95
	03	Hemorrhage Cramping		X						121 03/06/95
	24	Hemorrhage Hypotension Tachycardia			X	X		54		122 03/10/95
	23	Hemorrhage Orthostatic Hypotension	X	X	X			57		123 03/13/95
	02	Gunshot					X			123 03/13/95
	23	Hemorrhage Syncope Tachycardia Hypotension	X		X			52		124 04/11/95
	23	Vasovagal reaction			X					124 04/11/95
	23	Hemorrhage		X	X					124 04/11/95
	23	Hemorrhage Dizziness Shortness of Breath	X	X	X			51		124 04/11/95
	26	Hemorrhage Syncope/neck injury	X+				X	51		124 04/11/95
	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
	01	Hemorrhage	X+	X	X			50		125 04/19/95
	27	Pneumonia					X			132 06/07/95
	29	Hemorrhage Cramping Faintness	X				X	53		132 06/07/95
	04	Hemorrhage Dizziness		X						132 06/07/95
	04	Nausea Dizziness			X					132 06/07/95
	28	Hemorrhage	X	X			X	55		132 06/07/95
	28	Hemorrhage Vomiting Lightheaded	X		X		X	50		133 06/13/95
	23	Hemorrhage Vomiting Dizziness	X		X		X	55	Afro-Amer -ican	136 07/18/95
	28	Hemorrhage								136 07/18/95
	28	Hemorrhage	X				X	46		138 07/25/95
	28	Anxiety attack Depression Threatened suicide					X	50		139 07/28/95
	27	Viral meningitis					X			141 08/04/95
	28	Hemorrhage Passed out	X	X	X		X	60		143 08/09/95
	28	Hemorrhage (2 Med Watch reports)	X	X	X		X	62		143 08/09/95 144 08/10/95
	07	Abdominal pain	X					42		145 08/15/95
	07	Hemorrhage								145 08/15/95
	28	Hemorrhage Cramping	X	X	X		X	62		146 08/25/95
	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
	24	Hemorrhagia Cramping Fever Endometritis	X		X			61		149 09/21/95
	25	Hemorrhage Dizziness	X		X		X	60		154 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** **Faint/Dizziness** 20** **Cramping 14** **Vomiting 06** **Hypotension 05** **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.

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ON ORIGINAL

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
	22	199500076RU	Metrorrhagia Anemia	Vol. 1.66 p.32
		199500439RU	Metrorrhagia Abdominal pain	Vol. 3.2 p.10
	02	199500072RU	Metrohagia Vomiting Malaise	Vol. 1.66 p.32
	02	199500442RU	Dehydration Nausea Vomiting Diarrhea	Vol. 3.2 p.10
	02	199500074RU	Abdominal pain Anemia Metrorrhagia	Vol. 1.66 p.32
	02	199500075RU	Abdominal pain Metrorrhagia Anemia	Vol. 1.66 p.32
	01	199500071RU	Metrorrhagia Hypotension Anemia	Vol. 1.66 p.32
		199500440RU	Metrorrhagia Hypotension Headache	Vol. 3.2 p.10
	25	199500066RU	Metrorrhagia	Vol. 1.66 p.32
	25	199500067RU	Metrorrhagia	Vol. 1.66 p.32
	01	199500068RU	Hypotension	Vol. 1.66 p.32
	02	199500069RU	Urogenital Disorder	Vol. 1.66 p.32
	03	199500070RU	Metrorrhagia Syncope	Vol. 1.66 p.32
		199500444RU	Metrorrhagia Dizziness Headache	Vol. 3.2 p.10
	25	199500441RU	Abdominal Pain Hypotension	Vol. 3.2 p.10
		199500064RU	Metrorrhagia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
	03	199500065RU	Metrorrhagia Postural hypotension	Vol. 1.66 p.32
	26	199500077RU	Metrorrhagia	Vol. 1.66 p32
	01	199500102RU	Metrorrhagia	Vol. 1.66 p.32
	01	199500443RU	Vomiting Nausea Dizziness	Vol. 3.2 p.10
	01	199500104RU	Metrorrhagia	Vol. 1.66 p.32
	01	NA***	NA	Vol. 1.66 p.32
	04	199500106RU	Metrorrhagia	Vol. 1.66 p.32
	01	199500100RU	Metrorrhagia Fever	Vol. 1.66 p32
	01	199500101RU	Chest pain	Vol. 1.66 p.32
	03	199500140RU	Metrorrhagia	Vol. 1.66 p.32
	03	NA	NA	Vol. 1.66 p.32
	24	199500139RU	Metrorrhagia Hypotension	Vol. 1.66 p.32
	23	199500135RU	Metrorrhagia Postural Hypotension	Vol. 1.66 p.32
	02	NA	NA	Vol. 1.66 p.32
	23	199500175RU	Metrorrhagia Syncope	Vol. 1.66 p.32
	23	199500446RU	Syncope	Vol. 3.2 p.10
	23	199500447RU	Metrorrhagia	Vol. 3.2 p.10
	23	199500176RU	Metrorrhagia	Vol. 1.66 p.32
	26	199500172RU	Metrorrhagia Syncope	Vol. 1.66 p.32
	02	199500179RU	Metrorrhagia	Vol. 1.66 p.32
	01	NA	NA	Vol. 1.66 p.32
	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
	29	199500248RU	Metrorrhagia	Vol. 1.66 p.32
	04	199500249RU	Metrorrhagia	Vol. 1.66 p.32
	04	199500448RU	Dehydration	Vol. 3.2 p.10
	28	199500251RU	Metrorrhagia	Vol. 1.66 p.32
	28	199500455RU	Metrorrhagia	Vol. 3.2 p.10
	23	199500329RU 199500449	Vomiting Metrorrhagia Dizziness	Vol. 1.66 p.32 Vol. 1.66 p.32
	28	199500330RU	Metrorrhagia	Vol. 1.66 p.32
	28	199500454RU	Metrorrhagia	Vol. 1.66 p.32
	28	199500340RU	Depression	Vol. 1.66 p.32
	27	199500342RU	Meningitis	Vol. 3.2 p.10
	28	199500450RU 199500355RU	Metrorrhagia Hypotension Metrorrhagia Hypotension Anemia	Vol. 3.2 p10 Vol. 3.2 p.10
	28	199500356RU 199500451RU	Metrorrhagia Metrorrhagia	Vol. 3.2 p.10 Vol. 3.2 p.10
	07	199500365RU	Abdominal pain	Vol. 3.2 p.10
	07	199500366RU	Metrorrhagia	Vol. 3.2 p.10
	28	199500452RU	Metrorrhagia Uterine spasm	Vol. 3.2 p.10
	28	199500375RU	Abdominal pain Fever	Vol. 3.2 p.10
	24	199500453RU	Metrorrhagia Endometrial disorder	Vol. 3.2 p.10
	25	199500427RU	Metrorrhagia Malaise	Vol. 3.2 p.10

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

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115
July 11, 1996

The Honorable David A. Kessler, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Room 14-71 (HF-1)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

I have received your June 27, 1996 letter in partial response to my letter of May 23, 1996 regarding data integrity in clinical trials sponsored by the Population Council.

Your response raises further questions and a need for additional information. Accordingly, please provide the following by July 25, 1996:

(1) Please provide FDA's response to Dr. Bardin's December 7, 1994 letter on whether blood transfusions constitute a 3-day telephonic report to the Agency.

(2) Please provide all documents relating to a report about Patient No. 042 of Submission Serial Number 109 of IND ——

(3) Please provide a copy of Serial Number 107 of IND —— and the typed version of FDA 3500 form.

(4) The September 21, 1995 Associated Press article reported: "When asked if Louviere's patient qualifies as a serious complication, [Population Council spokesman Sandra] Waldman said it would be 'within the context of what happened before.' She said that in France, 0.1 percent of women using RU-486 bled to an extent that they needed transfusions. . . . Women participating in the test were told there was a small chance of excess bleeding." Given that history, why did the sponsor not ask the Agency about whether blood transfusions constituted a 3-day telephonic report to the Agency until after an adverse event report was submitted? Why wasn't this reporting issue anticipated?

(5) All unexpurgated books, records (including FOIA requests), correspondence, notes,

phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCs or on file servers that are part of local area or wide area networks) mentioning or pertaining to adverse events related to IND

If you have any questions, please contact Mr. Alan Slobodin of the Subcommittee staff at (202) 225-2927. I appreciate your cooperation in this matter.

Sincerely,

Joe Barton

Joe Barton
Chairman
Subcommittee on Oversight
and Investigations

JB:as

cc: The Honorable Thomas J. Bliley, Jr., Chairman

The Honorable John D. Dingell, Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

APPEARS THIS WAY
ON ORIGINAL

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]

Sincerely,

/S/

[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]

[redacted] – FDA

APPEARS THIS WAY
ON ORIGINAL

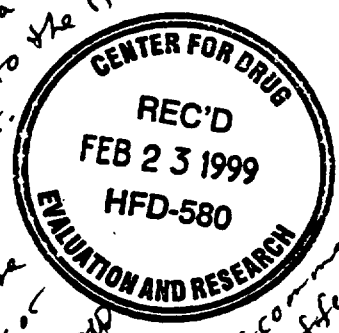
ORIGINAL

NEW CORRES

The Danco Group

BC

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



February 22, 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 019 – Response to FDA Letter of January 27, 1999
- Correspondence Regarding Teleconference Call of February 10, 1999 with _____ and _____

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.

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

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

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

CSO INITIALS 2/10/99

Sincerely,

/S/

President and
Chief Executive Officer

CC:

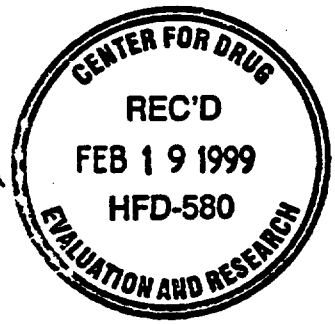
Sandra P. Arnold – Population Council

– FDA

ORIGINAL
NEW CORRESP

The Danco Group

noted. response to sponsor during 2/10/99 T-con. 151 2/23/99



February 8, 1999

Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products
Room ——— 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 ——————— letter of January 27, which commented on the Population Council's submissions of August 5 and September 24, 1997. These submissions represent the Gedeon Richter bulk substance manufacturing CMC.

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

The questions are:

[redacted]

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

Sincerely,

/S/

President and
Chief Executive Officer

Cc: [redacted]
Sandra P. Arnold – Population Council

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A. ☐ MEMO

/S/ 2/26/99

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

DF

NDA 20-687

JAN 27 1999

The Population Council
Attention: Harold Nash, Ph.D.
Senior Scientist
1230 York Avenue
New York, NY 10021

Dear Dr. Nash:

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

We also refer to your submissions dated August 5 and September 24, 1997, which provided for chemistry manufacturing and controls information.

We have completed our review of your submission and have the following comments and requests for information:

If you have any questions, contact [redacted] Project Manager, [redacted]

Sincerely.

/S/ 1/27/99

Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/ [redacted]
HFD-580/ [redacted] 1.20.99/n20687.ir
Concurrence — 1.20.99/ — 1.21.99/ — 1.22.99

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 18 1999

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

Dear Dr. Haskell:

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

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

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

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

Sincerely,

[redacted]
151

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 12 1999

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

Dear Dr. Poppema:

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

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

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

Sincerely yours,

151

———

———

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

ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

NEW CORRESP

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

noted
1.5.1
12/20/98

December 8, 1998

VIA FEDERAL EXPRESS

Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products
Room —— 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 —— name to end in "y";
- Please add —— 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 —— of bulk drug substance, pending resolution of manufacturing issues."

- Discussion of Dose Changes - mifepristone and misoprostol

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

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

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

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

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

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

Post Meeting Note
The reference to NDA —— should be to NDA 20-687.

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

Very truly yours,

Sandra Arnold

cc: ———————
———————
———————
Frederick H. Schmidt, Ph.D.
Patricia C. Vaughan, Esq.

APPEARS THIS WAY
ON ORIGINAL

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

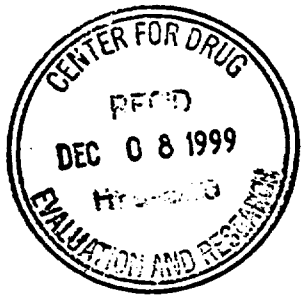
One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0500 Facsimile: (212) 755-6052 Email: pubinfo@popcouncil.org http://www.popcouncil.org

ORIGINAL

The Danco Group

ORIG AMENDMENT
BC

December 7, 1999



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

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

Dear ———

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

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

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

Sincerely,

/S/

President and
Chief Executive Officer

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

spulation Council

Sandra P. Arnold
Vice President
Corporate Affairs

NC

NEW CORRESP

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

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: samold@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?

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

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

VI. Discussion of commercial sources producing ———————— 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.

[redacted]

Very truly yours,

for Andrea Arnold

cc:

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

APPEARS THIS WAY
ON ORIGINAL

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

ORIG AMENDMENT
BC

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

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

June 25, 1998

Transmitted via Federal Express

Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products
Room ———, 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 015
- **Correspondence regarding recent telephone discussions between ——— and ———**
- **Request for meeting**

Dear ———

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

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

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

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

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

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

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

Very truly yours,

Sandra P. Arnold

Sandra P. Arnold
Vice President
Corporate Affairs

APPEARS THIS WAY
ON ORIGINAL

Cc: _____
_____
_____

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

JUN 27 1996

The Honorable Joe Barton
Chairman
Subcommittee on Oversight and Investigations
Commerce Committee
House of Representatives
Washington, D.C. 20515

Dear Chairman Barton:

This is in response to your letter of May 23, 1996, regarding a clinical trial sponsored by the Population Council that was reported by the Associated Press in an article on September 2, 1995. You expressed concerns regarding whether public information about the clinical trial is consistent with data filed with the Food and Drug Administration (FDA) and regarding the truth in reporting clinical data.

The newspaper article referenced in your letter reported that there had been no complications among the subjects in the clinical trial. The Population Council has never represented to FDA that RU-486 (mifepristone) is without potential complications. The complications that are described in this article, while unfortunate and rare, are not unexpected complications. FDA can confirm that the specific adverse event cited by Dr. Mark Louviere was reported to FDA precisely as described by Dr. Louviere in the news article and was reported in a timely manner by the sponsor. A copy of this adverse event report is enclosed with this letter.

FDA is currently reviewing this adverse event report, and all other submitted information and data, as part of our evaluation of the new drug application submitted for mifepristone by the Population Council. Please be assured that, as with all drug applications, the application and the documentation from the mifepristone clinical trials are being reviewed in accordance with stringent scientific and legal standards.

This letter and the enclosed adverse event report contain confidential information and other privileged information not releasable to the public under the Freedom of Information regulations promulgated by FDA. We request that the Subcommittee not publish or otherwise make public any part of this letter or any information contained within it.

Thank you for your interest and concern in raising this matter to our attention. We trust that this response addresses your concerns. If you have any further questions, please let us know.

Sincerely,

Sharon Smith Holston
Deputy Commissioner
for External Affairs

5 Enclosures
Adverse Event Report dated December 1, 1994
Associated Press article, September 2, 1995
Associated Press article, September 21, 1995
The Des Moines Register, September 21, 1995
Waterloo Courier, Sunday, September 23, 1995

cc: The Honorable Thomas J. Bliley, Jr.
Chairman

The Honorable John D. Dingell
Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Biomedical Research

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

ORIGINAL

December 7, 1994

Noted
12/14/94
/S/

BY FEDEX

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

Subject: IND ——— Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

Noted
12/14/94
/S/

Dear ———

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to ——— of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Bardin

C. Wayne Bardin

CWB:sh

CENTER FOR DRUG
REC'D
DEC 0 9 1994

REVIEWS COMPLETED

CSO [illegible]:

☐ [illegible] ☐ N.A.I.

/S/ 12/16/94

CSO INITIALS / DATE

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014. Expiration Date: November 30, 1995. See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
The Population Council

2. DATE OF SUBMISSION
December 07, 1994

3. ADDRESS (Number, Street, City, State and Zip Code)
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER (Include Area Code)
(212) 327-8717

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)
Mifepristone Tablets

6. IND NUMBER (If previously assigned)
IND —

7. INDICATION(S) (Covered by this submission)
Induction of abortion

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 109

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☒ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION

☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☐ OTHER _____ (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW: REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

PREVIOUS EDITIONS OBSOLETE.

FORM FDA 1571 (12/92)

12 CONTENTS OF APPLICATION

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

- ☐ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED Please refer to Submission 100

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

C. Wayne Bardin, MD
Vice President and Director
The Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

C. Wayne Bardin, MD
Vice President and Director
The Population Council

Irving M. Spitz, MD
Senior Scientist
The Population Council

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
C. Wayne Bardin, MD	C. Wayne Bardin
18. ADDRESS *(Number, Street, City, State and Zip Code)*	**19. TELEPHONE NUMBER** *(Include Area Code)* / **20 DATE**
1230 York Avenue New York, NY 10021	(212) 327-8717 / 12/07/94

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec 1001.)

Public reporting burden for this collection of information is estimated to average 100 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:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-H
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

May 23, 1996

The Honorable David A. Kessler, M.D.
Commissioner
Food and Drug Administration
Room 1471
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

Pursuant to Rules X and XI of the Rules of the U.S. House of Representatives, the Subcommittee is investigating FDA's handling of data integrity issues related to clinical trials. Under 21 CFR § 312.62(b), an investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with an investigational drug or employed as a control in the investigation. Under 21 CFR § 312.64(b), an investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. The Subcommittee has received credible information raising a question of whether such procedures were followed in a clinical trial.

According to an article in the September 21, 1995 Des Moines Register, Mark Louviere, M.D., of Waterloo, Iowa, stated that one of his patients who participated in a clinical trial sponsored by the Population Council lost more than half her blood, came close to death and needed surgery two weeks after taking an investigational new drug. Dr. Louviere said he saw an article in the Associated Press reporting that the clinical trial of the investigational new drug had concluded and that there had been no complications among the subjects in the clinical trial. Dr. Louviere stated: "If near-death due to the loss of half of one's blood volume, surgery and a transfusion of four units of blood do not qualify as a complication, I don't know what does." Statements from a clinical investigator and the sponsor are unclear about whether the adverse event mentioned by Dr. Louviere has been acknowledged. Dr. Louviere's statements, if accurate, raise a question about whether public information about the clinical trial is consistent with data filed with FDA. Further, his statements raise the issue of truth in reporting clinical data.

96-4062

Please provide the Subcommittee by June 6, 1996 with the following:

(1) Identities of all sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(2) All IND applications of these sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(3) All unexpurgated books, records (including FOIA requests), correspondence, notes, phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCs or on file servers that are part of local area or wide area networks) mentioning or pertaining to the adverse event referred to by Dr. Louviere or any other adverse events related to the same investigational drug.

(4) If FDA confirms this was an unreported adverse event and that it was not reported to or by the sponsor, please explain how FDA plans to address this data integrity issue.

If you have any questions about this request, please contact Alan Slobodin of the Committee staff at (202) 225-2927. I appreciate your cooperation in this matter.

Sincerely,

Joe Barton
Chairman
Subcommittee on Oversight
and Investigations

cc: The Honorable Thomas J. Bliley, Jr., Chairman

The Honorable John D. Dingell, Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

TELEFAX

TO: Ann Robbins

FAX: 212 - 327 - 7676

PHONE:

FROM:

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX:

PHONE:

DATE: 9/11/96

PAGES: 2 (Inclusive)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Product

Memorandum

Date: 10 Sep. 1996

From: _____ HFD-580 /S/

Subject: Labeling deficiencies

To: NDA 20-687

The draft labeling in the original NDA submission was reviewed in Chemistry Review # 1 dated 20 June 1996 and it was noted that minor labeling changes might be necessary. Labeling deficiencies were not conveyed to the Applicant because it was considered likely that an Amendment would be submitted to correct some obvious omissions (e.g. the lack of a structure for mifepristone in the Description Section). However, no Amendments pertaining to the chemistry related sections of the labeling have been submitted. The purpose of this Memorandum is to identify labeling deficiencies to be conveyed to the Applicant.
In the Description section of the draft package insert, the chemical name of mifepristone should be corrected by replacing "B" with "β". The structure of mifepristone should also be included. In addition, missing information in the 'How Supplied ' section regarding imprinting and carton contents should be provided.

CONCLUSIONS AND RECOMMENDATIONS: Labeling: The Applicant should be requested to include the structure of mifepristone in the Description section of the Package Insert and to correct the chemical name of mifepristone by replacing "B" by "β". The missing information (regarding imprinting and carton contents) in the 'How Supplied' section should also be provided. In addition, the Applicant should be informed that if a Tradename is to be used to market the product, it must be submitted and approved prior to use.

cc: Orig. NDA 20-687
HFD 580/ Div. Files
HFD 580/ _____
R/D initialed by: /S/

Filename: _____

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TELEFAX

TO: Ann Robb...

FAX: 212 327-7678

PHONE: _____

FROM: _____

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: _____

PHONE: _____

DATE: 9/10/96

PAGES: 5 X (Inclusive)

DF

AUG 22 1996

NDA 20-687

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.

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely yours,

/S/ 8-16-96

[redacted]

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

cc:
Orig. NDA
HFD-580
HFD-580/ [redacted]
HFD-580/ '8.9,13,16.96/n20687.p4ir
concurrences: 8.13.96 8.13.96/ 8.15.96/ 8.16.96

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

Population Council
er for
edical Research

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

NEW CORRESP

VIA FEDEX

August 15, 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 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.

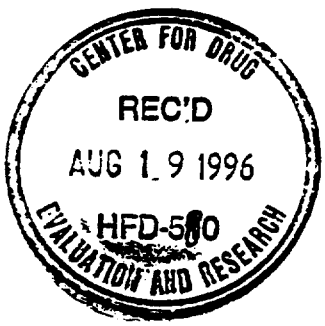
Please contact me if you have any questions or need further information.

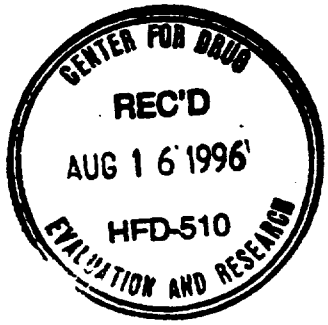
Best regards.

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR/yho





The Population Council
Center for
Biomedical Research

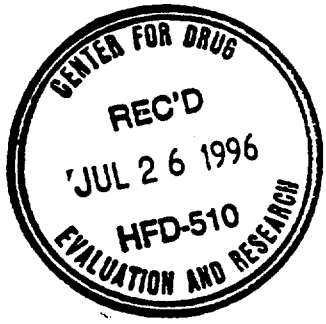
ORIGINAL

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

N1-34



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
CSO INITIALS DATE

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 16, 1996

[redacted]

Dear [redacted]

We have received and carefully considered your letter of July 10, 1996, to Commissioner Kessler concerning the upcoming meeting of the Advisory Committee for Reproductive Health Drugs to review the NDA for mifepristone. We want to assure you that FDA takes very seriously its obligation to ensure that its advisory committee meetings are free from any violation of Federal conflict of interest statutes or regulations.

FDA has assiduously screened all members of the advisory committee for possible issues under 18 U.S.C. § 208 and other authorities. Moreover, we have consulted with the HHS Office of the Special Counsel for Ethics (OSCE), which in turn consulted with the United States Office of Government Ethics (OGE). We are confident that all Federal ethics issues will be resolved appropriately.

Based on the advice received from OSCE, we would like to respond to the general legal questions you have raised:

First, you have questioned whether there may be a potential violation of 18 U.S.C. § 208 if any advisory committee member is an employee or committee member of an organization that receives compensation for abortion and related services. It is the legal opinion of OSCE, after consultation with OGE, that the matter scheduled for the advisory committee meeting would not have a "direct and predictable effect" on the financial interest of any individual or organization that is engaged in the provision of abortion and related services. 5 C.F.R. § 2635.402(b)(1). In keeping with past precedents, it was determined that any possible effect on the finances of such individuals or organizations as a result of the approval or nonapproval of mifepristone is "speculative," within the meaning of the implementing regulations, and therefore not covered by section 208. Id.

Second, section 208 generally does not have a bearing on individuals who are merely participants or "committee members" in a nonprofit organization. The financial interests of a nonprofit organization are not imputed to an individual unless the individual serves the organization in one of the specific fiduciary capacities listed in the statute, i.e., employee, officer, director, or trustee. See 18 U.S.C. § 208(a).

Third, although individuals who serve as "committee members" of a nonprofit organization generally are not covered by section 208, they may have a "covered relationship" with the organization, under the Federal regulation governing appearances and impartiality. See 5 C.F.R. § 2635.502(b)(1)(v). However, such a relationship cannot lead to an ethics violation unless it is with a party or the representative of a party to the Federal proceeding. See 5 C.F.R. § 2635.502(a). We would note that the party to this proceeding is the NDA sponsor, not the organizations to which your letter refers.

Fourth, you raise questions concerning the intellectual and philosophical views of certain individuals. It is important to remember that intellectual and philosophical views, even where published and well-known, do not constitute a "conflict of interest" under Federal ethics statutes and regulations. Indeed, the Office of Government Ethics has stated expressly that the rule governing appearances and impartiality must not "be construed to suggest that an employee should not participate in a matter because of his political, religious or moral views." 5 C.F.R. § 2635.502(b)(1)(Note).

Fifth, certain factual matters alleged in your letter appear to be inaccurate or incomplete, including certain matters pertaining to the executive secretary of the committee. For example, this individual is not an "employee" of the organization to which you refer, but rather an unpaid volunteer who performs services with that organization as an approved official duty professional development activity. Moreover, the participation of this individual in the 1988 meeting to which you refer was an official duty activity, not an outside activity; consequently, there is no conflict between his official duties and an outside interest or affiliation.[1]

Finally, based on consultation with FDA's Office of the Chief Counsel, we are confident that the advisory committee fully complies with 21 C.F.R. § 14.80. FDA makes a conscientious effort to achieve a reasonable balance of views and expertise on its advisory committees with respect to the scientific issues coming before the committees. We believe that we have achieved a reasonable balance of views and expertise on this committee, and that balance holds true with respect to the scientific issues raised by the mifepristone matter.

In conclusion, because we have no information that would suggest a colorable violation of any ethics law or regulation, we do not believe that an investigation is necessary or appropriate. With

---

[1] Your letter also states that this individual serves on an advisory panel of a nonprofit organization named in your letter. As noted above, however, mere participation in a nonprofit organization--as opposed to service as an employee, director, etc.--does not itself create a problem under 18 U.S.C. § 208. Additionally, the organization to which you refer is not the party to the FDA proceeding in this matter, within the meaning of 5 C.F.R. § 2635.502(a). As also noted above, the fact that an individual may have certain intellectual or philosophical views does not implicate the Federal ethics laws or regulations.

respect to your request for any written waiver determination, issued under 18 U.S.C. § 208(b), we would point out that such determinations, if ultimately issued in this case, may be requested according to the appropriate procedures found in the Freedom of Information Act and 18 U.S.C. § 208(d)(1). You should note also that, for administrative and other reasons, some of the individuals to whom you refer will not be participating in the mifepristone meeting, including

Sincerely,

151

[redacted]

Operations

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: July 18, 1996

TO: [redacted]
Financial Interest Review Section
Division of Ethics and Program Integrity

FROM: [redacted] /S/ [redacted]
Advisors and Consultants Staff, CDER

RE: July 19, 1996, Meeting of the Advisory Committee for Reproductive Health Drugs

On Friday, July 19, 1996, the Advisory Committee for Reproductive Health Drugs will meet in open session to discuss mifepristone (RU486) for the interruption of early pregnancy. The application is sponsored by The Population Council.

As directed, we have preformed a second conflict of interest screening of the participants for interests in Prostaglandin misoprostol, and the following companies:

G.D. Searle & Company, including Monsanto Company
Roussel UCLAF
Hoeschst AG
Gideon-Richter

In addition, the participants were asked whether they were serving as a compensated member, officer, trustee, etc., for Planned Parenthood or any other organization which, to their knowledge, advocates the approval of RU486 (mifepristone).

Below is a summary of the results of the screening for your consideration:

- Ezra C. Davidson, Jr., M.D., Chairman of the Committee, [redacted]

  Further, Dr. Davidson [redacted]

- Janet Daling, Ph.D., [redacted]

o Jane Zones, Ph.D.,

[redacted]

With respect to the other participants (Dr. Dr. Henderson, Dr. Lewis, Dr. Petitti, Dr. Kosasa, and Dr. O'Sullivan), they did not report any current financial interests or professional involvements with respect to misoprostol, G.D. Searle, including Monsanto, Roussel UCLAF, Hoechst AG, or Gideon-Richter. Further, they are not serving as a compensated employee, officer, etc., for Planned Parenthood or any other organization which, to their knowledge, advocates the approval of RU486.

In addition, because of his past involvement with respect to RU486, [redacted] will not be attending the advisory committee meeting. Further, [redacted] has advised us that he is unable to attend the meeting.

We are awaiting Deborah Narrigan's response to our second conflict of interest screening and will forward a description of her relevant interests, if any, under separate memorandum.

Please contact me at [redacted] if you have questions.

APPEARS THIS WAY
ON ORIGINAL

ROUTING AND TRANSMITTAL SLIP Date: July 12, 1996

1.

2.

3.

4.

5.

6.

cc:

	Action		File		Note & Return
	Approval		For Clearance		Per Conversation
	As Requested		For Correction		Prepare Reply
	Circulate	x	For Your Info.		Review
x	Comment		Investigate		See Me
	Coordinate		Justify		Signature

SUBJECT: ADDITIONAL QUESTIONS FROM MR. JOE BARTON RE: RU-486

REMARKS: Here is a follow-up set of questions from Chairman Joe Barton, Subcommittee on Oversight and Investigations, House Commerce Committee, in response to our letter to him of June 27, 1996, regarding an RU-486 clinical trial that had reported an adverse reaction.

Please note he asks further questions based on the ADR we sent him, as well as for all IND documents.

We will call you to set a meeting to discuss this matter at a later time.

From: Office of Legislative Affairs

Room No.:

Phone Number:

JUN 27 1996

The Honorable Joe Barton
Chairman
Subcommittee on Oversight and Investigations
Commerce Committee
House of Representatives
Washington, D.C. 20515

Dear Chairman Barton:

This is in response to your letter of May 23, 1996, regarding a clinical trial sponsored by the Population Council that was reported by the Associated Press in an article on September 2, 1995. You expressed concerns regarding whether public information about the clinical trial is consistent with data filed with the Food and Drug Administration (FDA) and regarding the truth in reporting clinical data.

The newspaper article referenced in your letter reported that there had been no complications among the subjects in the clinical trial. The Population Council has never represented to FDA that RU-486 (mifepristone) is without potential complications. The complications that are described in this article, while unfortunate and rare, are not unexpected complications. FDA can confirm that the specific adverse event cited by Dr. Mark Louviere was reported to FDA precisely as described by Dr. Louviere in the news article and was reported in a timely manner by the sponsor. A copy of this adverse event report is enclosed with this letter.

FDA is currently reviewing this adverse event report, and all other submitted information and data, as part of our evaluation of the new drug application submitted for mifepristone by the Population Council. Please be assured that, as with all drug applications, the application and the documentation from the mifepristone clinical trials are being reviewed in accordance with stringent scientific and legal standards.

This letter and the enclosed adverse event report contain confidential information and other privileged information not releasable to the public under the Freedom of Information regulations promulgated by FDA. We request that the Subcommittee not publish or otherwise make public any part of this letter or any information contained within it.

Thank you for your interest and concern in raising this matter to our attention. We trust that this response addresses your concerns. If you have any further questions, please let us know.

Sincerely,

Sharon Smith Holston
Deputy Commissioner
for External Affairs

5 Enclosures
Adverse Event Report dated December 1, 1994
Associated Press article, September 2, 1995
Associated Press article, September 21, 1995
The Des Moines Register, September 21, 1995
Waterloo Courier, Sunday, September 23, 1995

cc: The Honorable Thomas J. Bliley, Jr.
Chairman

The Honorable John D. Dingell
Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

The Population Council

Center for
Biomedical Research

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

ORIGINAL

December 7, 1994

Noted
12/14/94
/S/

BY FEDEX

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

Subject: IND # ——— - Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

Noted
/S/
16 Dec 94

Dear ———

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to ——— of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Rm

C. Wayne Ba

CWB:sh

CENTER FOR DRUG
REC'D
DEC 0 9 1994

REVIEWS COMPLETED

CSO [illegible]:

☐ [illegible] ☐ N.A.I.

/S/ 12/16/94

CSO INITIALS / DATE

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014. Expiration Date: November 30, 1995. See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
The Population Council

2. DATE OF SUBMISSION
December 07, 1994

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 327-8717

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Mifepristone Tablets

6. IND NUMBER *(If previously assigned)*
IND —

7. INDICATION(S) *(Covered by this submission)*
Induction of abortion

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 109

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☒ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION

☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED

☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHANGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

PREVIOUS EDITIONS OBSOLETE.

12 CONTENTS OF APPLICATION

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

- ☐ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13 IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED Please refer to Submission 100

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

C. Wayne Bardin, MD
Vice President and Director
The Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

C. Wayne Bardin, MD
Vice President and Director
The Population Council

Irving M. Spitz, MD
Senior Scientist
The Population Council

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
C. Wayne Bardin, MD	C. Wayne Bardin	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1230 York Avenue New York, NY 10021	(212) 327-8717	12/07/94

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

TELEFAX

TO: Erin Robbins

FAX: 212 327-7677

PHONE: _____

FROM: _____

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

FAX: _____

PHONE: _____

DATE: 6/20/96

PAGES: 5 (Inclusive)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

JUN 20 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.

We have completed the Biopharmaceutics section of your pending NDA and have the following comments and requests for information:

1. You state in your proposed package insert that "drugs known to cause enzyme induction may reduce the efficacy of (mifepristone) due to increased metabolism." However, a full investigation of the enzymes involved in the metabolism of mifepristone was not submitted and an extensive search of the biomedical literature did not yield this information. If this information is available, we recommend it be submitted to the Agency. Alternatively, we suggest, though not required for an action on this application, that *in vitro* studies be carried out to fully identify the enzymes that catalyze the metabolism of mifepristone.

2. To support the rationale for using the dissolution medium and volume plus the selected paddle rotation speed of 75 rpm for the proposed dissolution method, the following information should be provided:

   a. pH solubility data for mifepristone;

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

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

   d. Raw data and profiles at different paddle rotation speeds (50 rpm and 75 rpm) in the dissolution media cited above.

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

Sincerely yours,

/S/ 6-20-96

[redacted]

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

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

The Population Council

Center for
Biomedical Research

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

June 20, 1996

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

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

Dear [redacted]

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

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

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

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

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

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

Sincerely yours,

Ann Robbins

Ann Robbins, PhD
Scientist

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF THE CENTER DIRECTOR
EXECUTIVE OPERATIONS STAFF

DATE: 5/29/96

TO: _____

PHONE: _____ FAX: _____

FROM: /S/

PHONE: _____ FAX: _____

TOTAL NUMBER OF PAGES: 4
(EXCLUDING COVER SHEET)

COMMENTS:

Meeting to discuss this document request will be held in [illegible] at 3:00 p.m., Thurs., May 30th.

Thanks,

/S/

U.S. House of Representatives
Committee on Commerce
Room 2125, Rayburn House Office Building
Washington, DC 20515–6115

May 23, 1996

The Honorable David A. Kessler, M.D.
Commissioner
Food and Drug Administration
Room 1471
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

Pursuant to Rules X and XI of the Rules of the U.S. House of Representatives, the Subcommittee is investigating FDA's handling of data integrity issues related to clinical trials. Under 21 CFR § 312.62(b), an investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with an investigational drug or employed as a control in the investigation. Under 21 CFR § 312.64(b), an investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. The Subcommittee has received credible information raising a question of whether such procedures were followed in a clinical trial.

According to an article in the September 21, 1995 Des Moines Register, Mark Louviere, M.D., of Waterloo, Iowa, stated that one of his patients who participated in a clinical trial sponsored by the Population Council lost more than half her blood, came close to death and needed surgery two weeks after taking an investigational new drug. Dr. Louviere said he saw an article in the Associated Press reporting that the clinical trial of the investigational new drug had concluded and that there had been no complications among the subjects in the clinical trial. Dr. Louviere stated: "If near-death due to the loss of half of one's blood volume, surgery and a transfusion of four units of blood do not qualify as a complication, I don't know what does." Statements from the clinical investigator and the sponsor are unclear about whether the adverse event mentioned by Dr. Louviere has been acknowledged. Dr. Louviere's statements, if accurate, raise a question about whether public information about the clinical trial is consistent with data filed with FDA. Further, his statements raise the issue of truth in reporting clinical data.

96-4062

Drug → RU-486

Obtain copy of newspaper article.

Please provide the Subcommittee by June 6, 1996 with the following:

(1) Identities of all sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(2) All IND applications of these sponsors or subsponsors of the investigational new drug related to the adverse event referenced by Dr. Louviere.

(3) All unexpurgated books, records (including FOIA requests), correspondence, notes, phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCs or on file servers that are part of local area or wide area networks) mentioning or pertaining to the adverse event referred to by Dr. Louviere or any other adverse events related to the same investigational drug.

(4) If FDA confirms this was an unreported adverse event and that it was not reported to or by the sponsor, please explain how FDA plans to address this data integrity issue.

If you have any questions about this request, please contact Alan Slobodin of the Committee staff at (202) 225-2927. I appreciate your cooperation in this matter.

Sincerely,

Joe Barton
Chairman
Subcommittee on Oversight
and Investigations

cc: The Honorable Thomas J. Bliley, Jr., Chairman

The Honorable John D. Dingell, Ranking Minority Member

The Honorable Ron Klink, Ranking Minority Member
Subcommittee on Oversight and Investigations

NDA 20-687

MAY 20 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.

We have completed our initial review of your submission and have the following comments from the Division of Pharmaceutical Evaluation II.

1. The "Pharmacokinetics/Metabolism" portion of the CLINICAL PHARMACOLOGY section of the proposed labeling should be formatted to contain subsections entitled; "Absorption", "Distribution", "Metabolism", "Excretion", and "Special Populations" with "Hepatically Impaired Patients" and "Renally Impaired Patients" as subheadings.

2. It is stated in the proposed package insert that "drugs known to cause enzyme induction may reduce the efficacy of (mifepristone) due to increased metabolism." However, a full investigation of the enzymes involved in the metabolism of mifepristone was not submitted and an extensive search of the biomedical literature did not yield this information. It is suggested, although not required, that in vitro studies be carried out to fully identify the enzymes that catalyze the metabolism of mifepristone.

If you have any questions concerning this IND, please contact ——— CSO ———

Sincerely yours,

/S/ 5/17/96

Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

TELEFAX

TO: Dr. Rosa

FAX: 212 327-7677

PHONE:

FROM:

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

FAX:

PHONE:

DATE: 5/3/96

PAGES: 2 (Inclusive)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

MAY - 7 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 14, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifepristone Oral Tablets, 200 mg.

We also refer to our acknowledgement letter dated March 20, 1996, which stated that the review priority classification for this application would be standard (S).

Our determination of the review priority classification is based on information available on the new drug and on alternate treatments already marketed for the proposed indication. Upon further consideration of your application, we have concluded that it should receive a priority (P) review.

If you have any questions, please contact ———————

Sincerely yours,

/S/

———; Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

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

Number of Pages (including this sheet): 2

Send to Facsimile Number: ———

Date: 7 May 1996

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

Send to Person: ———

Subject: Request for meeting

Dear ———

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

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

Best regards,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

APPEARS THIS WAY
ON ORIGINAL

SUGGESTED AGENDA

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

2. Safety Update
   - timing
   - content

3. CMC
   - starting material
   - FDA inspection of manufacturer
   - information available about manufacturer under FOI
   - status of new manufacturer of active ingredient and dosage form

4. Advisory Committee Meeting

5. FDA Audit of the French Clinics

6. Data from the U.S. Trials

APPEARS THIS WAY
ON ORIGINAL

TELEFAX

TO: Alan Robins

FAX: 212 327-7678

PHONE: _____

FROM: _____

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

FAX: _____

PHONE: _____

DATE: 4/24/96

PAGES: 2 (Inclusive)

Comments: [redacted] cannot be considered a starting material for the synthesis of mifepristone. This is not a commercially available material and, as stated by the Sponsor on page 254, vol. 18.1, (Amendment of 27 Oct. 1995) its structural characteristics are not described in the literature . Its synthesis is described only in the patent literature.
Full step-by-step details of the synthesis of [redacted] should be provided from simpler, commercially available starting materials which have been well characterized in the literature. [redacted] in mifepristone are already established in [redacted] and consequently, assurance that undesired [redacted] are adequately controlled is necessary. Three potential impurities in [redacted] have been identified (page 98, vol. 18.1, Amendment of 27 Oct. 1995); however, it is not obvious why the [redacted] has not been included in this list. Tests for residual solvents are also necessary. Since this is an optically active compound, enantiomeric purity, using a method which will distinguish one enantiomer from another, should be determined or, evidence provided that the undesired enantiomer is not carried through the synthesis to give products that contaminate the drug substance.

Cleared for Faxing: /S/

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Medical Research

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

April 19, 1996

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

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

Dear ———

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

NDA Item 4 - Samples, Methods Validation and Labeling

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

NDA Item 8 - Clinical Data Section

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

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

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

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

Attachments: Described above.

NDA 20-687

MAR 20 1996

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

Dear Dr. Robbins:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Mifepristone 200 mg Oral Tablets

Therapeutic Classification: Standard

Date of Application: March 14, 1996

Date of Receipt: March 18, 1996

Our Reference Number: 20-687

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 17, 1996, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Consumer Safety Officer
Telephone:

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 3-19-96

Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-687
HFD-510/Div. Files
HFD-80
HFD-510/ March 19, 1996/n20687.ak
concurrence: 3.19.96

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

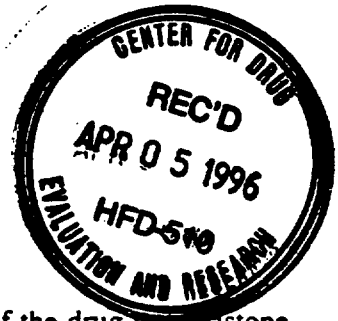
The Population Council

Center for
Medical Research

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

March 14, 1996

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



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

Dear Madam/Sir:

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

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

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

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

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

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

Attachment: User fee coversheet form 3397
NDA 20-687

The Population Council

Center for
Biomedical Research

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

ORIGINAL

December 7, 1994

Noted
12/14/94
/S/

BY FEDEX

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

Subject: IND —— - Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

Noted
/S/
16 Dec 94

Dear ——

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to ———— of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council (Patient ID No. 027, pp. 01-02); (2) a report of a subject hospitalized for general weakness (No. 042, pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

Please advise us if blood transfusions constitute a 3-day telephonic report to the Agency.

If you have require any additional information please contact me.

Sincerely,

CW Ba

C. Wayne Ba

CWB:sh

CENTER FOR DRUG
REC'D
DEC 0 9 1994

REVIEWS COMPLETED

—— IN:

☐ LET ☐ N.A.I.

/S/ 12/16/94

—INITIALS / DATE

T

SWIDLER & BERLIN

CHARTERED

LESTER S. HYMAN
OF COUNSEL

DIRECT DIAL
(202)424-7509

April 25, 1994

Advisor to the Commissioner
Food & Drug Administration
14-71 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear

As you requested, I enclose, on behalf of Roussel Uclaf, an agenda of items for discussion by Dr. Kessler and Professor Afting on May 6th.

Roussel appreciates the constructive offer made by Dr. Kessler at our April 14th conference with Secretary Shalala to meet and cooperate with Roussel in every way possible to try and find appropriate solutions to the problems we discussed.

Always sincerely,

Lester S. Hyman

Enclosure

LSH:lsj:3455.01

5010427.1

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(202)424-7500 ■ TELEX 701131 ■ FACSIMILE (202)424-7643