ROUSSEL UCLAF

I

TELEFAX

De/from:	[redacted] Direction de la Communication	Tel. (1) 40 62 44 34 Fax. (1) 40 62 44 90
A/to:	[redacted] Department of Health & Human Services FDA - Rockville (USA) - Fax [redacted]	
Date:	February 26, 1993	Page(s): 1+6

Dear [redacted]

Re:- **RU 486 - Agreement between the Population Council and Roussel Uclaf**

Following your discussion with Dr. Sakiz, please find attached copy of his letter dated July 18, 1984, to Dr. C. Wayne Bardin, at the Population Council, stating that "...in addition to the rights granted to the Council under the Agreement, Roussel is willing to grant the Council the right to arrange for sales of products (as defined in the Agreement) to public sector organizations for distribution in the United States of America on the other terms set forth in the Agreement notwithstanding the exclusion of the United States from Territory (as defined in the Agreement)."

Also enclosed is a copy of the agreement signed on July 17, 1984 between the Population Council and Roussel Uclaf referred to in the above letter.

I am at your disposal for any further information which you may require, and remain,

Yours sincerely,

151

Boite Postale: 120.07
75323 Paris Cédex 07

Paris, on July 18, 1984

Annexe IV

THE POPULATION COUNCIL, INC.
Center for Biomedical Research
1230 York Avenue
NEW YORK, N.Y. 10021
U.S.A.

Attention to Dr. C. Wayne BARDIN

Dear Sirs,

Reference is made to the Agreement, dated as of July 17, 1984, (the "Agreement"), between the POPULATION COUNCIL, INC. (the "COUNCIL") and ROUSSEL-UCLAF S.A. ("ROUSSEL").

We understand that in addition to the rights granted to the COUNCIL under the Agreement, ROUSSEL is willing to grant the COUNCIL the right to arrange for sales of Products (as defined in the Agreement) to public sector organizations for distribution in the United States of America on the other terms set forth in the Agreement notwithstanding the exclusion of the United States from Territory (as defined in the Agreement). The term "public sector organization" for this purpose shall include entities based in the United States nominated by the COUNCIL and approved by ROUSSEL, such approval not to be unreasonably withheld. ROUSSEL shall be entitled in connection with each nomination made by the COUNCIL hereunder to request written information demonstrating that the nominee qualifies as a public sector organization and the COUNCIL shall have a reasonable amount of time following receipt of any such request in which to provide such information.

If you agree with the foregoing, would you please return to us a copy of this letter accepted on behalf of your company, dated and signed.

Thanking you in advance, we remain,

Sincerely yours,

Dr. E. SAEZ

Accepted by : THE POPULATION COUNCIL, INC.

/S/

HFD-150

MEMORANDUM OF MEETING
March 2, 1993, at 3:30 p.m.

ATTENDEES: See attached list

SUBJECT: Initiatives to promote the testing in the United States of Mifepristone (RU-486) and other antiprogestins

The Food and Drug Administration initiated this meeting to discuss with the National Institutes of Health initiatives that were ongoing, and which could be planned, to respond to the President's directive to assess initiatives by which the Department can promote the testing in the United States of RU-486 and other antiprogestins.

Representatives from the National Institute of Child Health and Human Development (NICHD) provided the following information:

1. On February 5, 1993, NICHD published a Program Announcement inviting the submission of investigator-initiated research grant applications to conduct basic research on antiprogestins and to explore the potential clinical utilization of antiprogestins in the treatment of a variety of reproductive disorders as well as for contraception. The purpose of this initiative is to stimulate research that will attempt to further characterize and define the mechanism(s) of action of antiprogestins, their use for treatment of disorders of the reproductive system, and their utility for application as contraceptive agents or in facilitating parturition. Examples of research topics that would be considered responsive to this solicitation include studies on reproductive health, reproductive disorders (endometriosis, fibroids), contraceptives (including the morning-after pill), cervical ripening, etc.

A Program Announcement (PA) is unlike a Request for Applications (RFA) in that, for a PA, no funding has been set aside, no Study Section has been designated, etc.; a PA is only an announcement of interest for potential funding. NICHD will analyze the responses received. If the applications are adequate, no RFA is necessary. If there are insufficient applications submitted on a given topic, NICHD could publish a Request for Proposals on that topic(s).

2. The Hyde Amendment, in DHHS's appropriation, prohibits the use of agency funds to "be used to perform abortions except where the life of the mother would be endangered if the fetus were carried to term." The specific language of the Hyde Amendment has varied from year to year. As currently worded, NIH could gather data related to the consequences or effects of abortion; however, it could not use its funds to pay for the performance of abortions. (Title X is no longer a limiting factor, because when it was renewed, the NICHD appropriation for population research was no longer under it.)

3. NICHD has talked with Roussel-Uclaf about RU-486, and with Schering about other antiprogestins under development. Both companies indicated their interest in supplying these drugs for preclinical and clinical testing. However, Schering indicated that it would not supply drugs for preclinical or clinical testing for an abortifacient indication. In discussing the various indications under study for RU-486, NICHD indicated that while the original optimism for its usefulness in ——— has not yet been proven and it did not appear to be helpful in treating ———. there remained a theoretical basis for optimism concerning its analogs, particularly for obstetrical uses such as induction of labor.

4. The World Health Organization is conducting a dose response study of RU-486 to determine whether the 600 mg. dose currently in clinical use is the optimal dose. ———

5. NICHD ——— antiprogestins for post-coital use. In order to issue an RFP for a post-coital contraceptive drug (morning-after pill), funding would need to be set aside. There was some discussion of using the Population Council's IND as an alternate to a master file for post-coital clinical studies and problems that individual investigators may have with that approach.

6. In order for NICHD to support research involving RU-486, a clinical investigator and Roussel-Uclaf would need to start the process by submitting a research application to NIH. NICHD could respond to such a request following its peer review, and assuming that it scored well in the peer review process. This process takes approximately 9 months. For use as an abortifacient, given the Hyde Amendment, NIH could conceivably monitor a study, receive case report forms, analyze data, etc., but NIH could not fund the abortifacient activity itself. NICHD is willing to be involved in this type of activity, but indicated its preference for an effort to test and market RU-486 as a ———

Representatives from the National Cancer Institute (NCI) provided the following information:

1. NCI has met several times in the last two years with Roussel-Uclaf. Results from studies of Cushing's disease appear good but this is a rare disease.

2. NCI has no plans at present to study RU-486 for ——— The data from European and Canadian studies will be followed closely.

3. NCI is serving as a drug distribution resource for study of RU-486 in the ——— sponsored under his own IND. He has completed a Phase I study; it is too early to determine its effectiveness for this indication. NCI discussed with Roussel-Uclaf a compassionate use mechanism for patients ineligible for ——— study; Roussel-Uclaf declined the offer.

The representative from NIH's Office of Research on Women's Health (ORWH) provided the following information:

1. The ORWH funds research in women's health in collaboration with each of the Institutes and Centers of the NIH. Proposals are considered for ORWH funding only after they are submitted to a specific institute or center and undergo peer review. The ORWH has not funded RU-486 research because proposals have not been submitted by an institute or center. However, the ORWH will consider funding future research in this area.

/S/

Senior Policy Analyst
Office of the Executive Secretariat

Attachment

APPEARS THIS WAY
ON ORIGINAL

March 2 Meeting Attendees
3:30 p.m., Room 14-94

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development (NICHD)

Center for Population Research, NICHD
[Attending for

NCI

Cancer Therapy Evaluation Program, NCI

Office of Research on Women's Health, Office of the Director
[Attending for

FOOD AND DRUG ADMINISTRATION

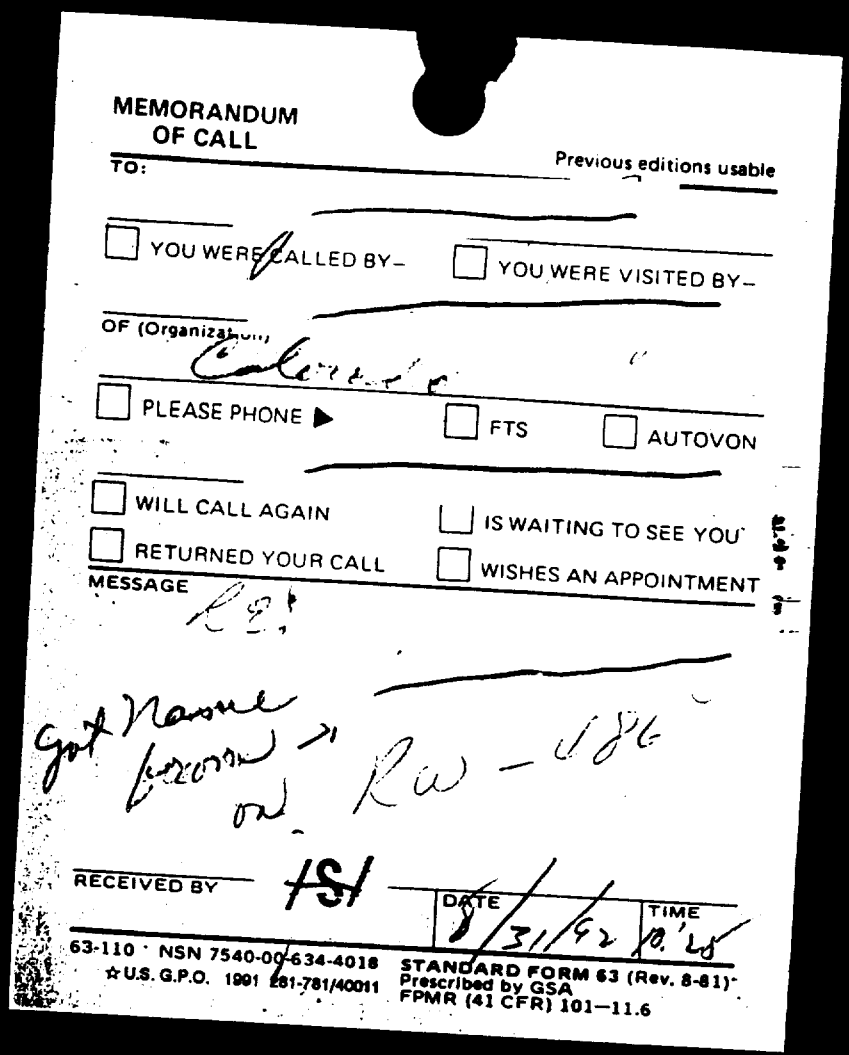
Center for Drug Evaluation and Research (CDER)

Division of Metabolism and Endocrine Drug Products
CDER

Division of Metabolism and Endocrine Drug Products, CDER

Division of Oncology and Pulmonary Drug Products, CDER

Executive Secretariat



MEMORANDUM
OF CALL

Previous editions usable

TO:

☐ YOU WERE CALLED BY— ☐ YOU WERE VISITED BY—

OF (Organization)

☐ PLEASE PHONE ▶ ☐ FTS ☐ AUTOVON

☐ WILL CALL AGAIN ☐ IS WAITING TO SEE YOU

☐ RETURNED YOUR CALL ☐ WISHES AN APPOINTMENT

MESSAGE

Got Name known → on RW - 086

RECEIVED BY /S/

DATE 8/31/92 TIME 10:45

63-110 · NSN 7540-00-634-4018 STANDARD FORM 63 (Rev. 8-81)
☆U.S. G.P.O. 1991 281-781/40011 Prescribed by GSA
FPMR (41 CFR) 101—11.6

MIF 004407

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20687/000
Stamp: 18-MAR-1996
Regulatory Due: 19-FEB-2000
Applicant: POPULATION COUNCIL
1230 YORK AVE
NEW YORK, NY 10021
Priority: 1P
Org Code: 580

Action Goal:
District Goal: 17-JAN-1997
Brand Name: MIFEPRISTONE 200MG TABS
Estab. Name:
Generic Name: MIFEPRISTONE 200MG TABS

Dosage Form: (TABLET)
Strength: 200 MG

Application Comment:
FDA Contacts: (HFD-580) Project Manager
(HFD-580)
(HFD-580) Team Leader

Overall Recommendation: WITHHOLD on 20-DEC-1999 by
WITHHOLD on 14-FEB-2000 by

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-SEP-1999				
OC RECOMMENDATION	01-SEP-1999			ACCEPTABLE BASED ON PROFILE	
ASSIGNED INSPECTION	14-OCT-1999	PS			
DO RECOMMENDATION	19-OCT-1999			WITHHOLD INADEQUATE LAB CONTROLS	
EIR RECEIVED BY OC	11-JAN-2000				
INSPECTION PERFORMED	14-FEB-2000		11-FEB-2000		
DO RECOMMENDATION	14-FEB-2000			ACCEPTABLE INSPECTION	
OC RECOMMENDATION	14-FEB-2000			ACCEPTABLE DISTRICT RECOMMENDATION	

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	01-SEP-1999				

SUBMITTED TO DO 01-SEP-1999 PS
ASSIGNED INSPECTION 17-SEP-1999 PS
DO RECOMMENDATION 19-OCT-1999 WITHHOLD
EQUIPMENT QUALIFICATION
INSUFFICIENT DEVELOPMENT
DATA

DO RECOMMENDATION 17-DEC-1999 ACCEPTABLE
ADEQUATE FIRM RESPONSE
RESPONSE TO FDA-483 WAS ADEQUATE, NO REINSPECTION NEEEDED.
OC RECOMMENDATION 20-DEC-1999 ACCEPTABLE
DISTRICT RECOMMENDATION

Establishment: 9610721
HOECHST MARION ROUSSEL
63480
VERTOLAYE, , FR
DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment: CSN; PLANT 2 (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-APR-1996				EES_CONV
OC RECOMMENDATION	23-APR-1996			ACCEPTABLE BASED ON PROFILE	EES_CONV

Establishment: 9611688
HOECHST MARION ROUSSEL
60200
COMPIEGNE, CEDEX, FR
DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
Estab. Comment: MFG; NME PRODUCT (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-APR-1996				EES_CONV
OC RECOMMENDATION	14-MAY-1996			BASED ON FILE REVIEW	EES_CONV

NO OC RECOMMENDATION FOR HISTORICAL DATA

Establishment: 9610109
ROUSSEL UCLAF
102, RT DE NOISY, 93200
ROMAINVILLE, , FR
DMF No: AADA:
Responsibilities:
Profile: TCM OAI Status: NONE
Estab. Comment: MFG; NME PRODUCT (on 24-AUG-1996 by EES_CONV)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-APR-1996				EES_CONV
OC RECOMMENDATION	14-MAY-1996			BASED ON FILE REVIEW	EES_CONV

NO OC RECOMMENDATION FOR HISTORICAL DATA

Establishment: 9615606

SHANGHAI HUALIAN PHARMACEUTICAL CO LTD
MINLE ROAD PUDONG DEVELOPMENT AREA
SHANGHAI, , CH 201419

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: THIS IS THE NEW MANUFACTURER FOR THE BULK DRUG SUBSTANCE. THE SPONSOR HAS STATED THAT THIS FACILITY WILL BE READY FOR INSPECTION IN JULY 1999. (on 17-MAY-1999 by (HFD-580)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-MAY-1999				
SUBMITTED TO DO	18-MAY-1999	GMP			
ASSIGNED INSPECTION	18-MAY-1999	GMP			
INSPECTION SCHEDULED	21-SEP-1999		27-OCT-1999		
INSPECTION PERFORMED	01-NOV-1999		28-OCT-1999		
DO RECOMMENDATION	15-DEC-1999			WITHHOLD	
OC RECOMMENDATION	15-DEC-1999			DEVIATION FROM DMF/NDA/ANDA WITHHOLD	
				DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (*Check One*) ☒ Original ☐ Follow-Up ☐ FUR	DATE 17 April 1996	PHONE # [redacted]	EER ID # 10038
REQUESTOR'S NAME [redacted]	DIVISION Metabolism & Endocrine D. P.		MAIL CODE HFD-510
APPLICATION AND SUPPLEMENT NUMBER NDA 20-687			
BRAND NAME	ESTABLISHED NAME Mifepristone		
DOSAGE AND STRENGTH 200 mg tablets			STERILE ☐ YES ☒ NO
PROFILE CLASS TCM	PRIORITY CLASSIFICATION (*See SMG CDER-4820.3*) 1P		
APPLICANT'S NAME Population Council			
ADDRESS 1230 York Avenue, New York, NY 10021			
COMMENTS At the Div. Meeting on 17 April 1996 it was decided to change the priority classification for this Application from 1S to 1P. Consequently, the new goal date is 25 Aug. 1996. NME			UFD = 8/25/96 (HFD = ~~8/25/97~~)

FACILITIES TO BE EVALUATED

(Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CDE	F KEY/ CIRTS ID	HFD-324 USE ONLY	
ROUSSEL UCLAF PLANT 2 63480 Vertolaye, France	Manufacture of Drug Substance	DMF CSN	ROUV 24568	AC	6/27/95
2. USIPHAR Plant at Compiègne Route de Choisy-au--Bac 60205 Compiegne- FRANCE Compagnl	Manufacture of Drug Product NME	DMF TCM	ROUC 24569	AC	9/20/94
3. Roussel Uclaf Plant 1 102, route de Noisy 93235 Romainville France	Manufacture of Drug Product NME	 TCM	ROUR 24570	AC	4/15/96
4.					
5.					

FOR HFD-324 USE ONLY	CSO TST	DATE RECEIVED 4/22/96	
	CGMP COMPLIANCE STATUS acceptable	DATE 5/15/96	

EER Inspection For EER ID: 10038 & EER Type/#: N 020687

Facility: 42300 ROUSSEL UCLAF
ddress: 2124
VERTOLAYE, 63480

District:
Profile: CCS CHEMICAL SYNTHESIS CRUDE DRUG
Comment: CSN; PLANT 2
CFN: 9610721 DMF #: ——— Insp ID: 24568 Fac. Type: FOR

Inspection Source: PR ORA PROF
Inspection Request Date:
Inspection Date: 27-JUN-1995
Inspection Received:
CES Conclusion:

CSO:
Assigned:
Completed:
CSO Review Status:
To District-Final:
Rec'd District-Final:

Status/Date: CM COMPLETE 23-APR-1996

CTRL H = Previous Block; CTRL N = Next Block; F4 = Exit;
Press RETURN to go to the Comment field.
Count: *1

<Replace>

EER Inspection For EER ID: 10038 & EER Type/#: N 020687

Facility: 42300 ROUSSEL UCLAF
ddress: 30846
COMPIEGNE, FR

District:
Profile: TCM TABLETS, PROMPT RELEASE
Comment: MFG; NME PRODUCT
CFN: 9611688 DMF #: ———— Insp ID: 24569 Fac. Type: FOR

Inspection Source: FF FOR FILE
Inspection Request Date:
Inspection Date: 20-SEP-1994
Inspection Received:
CES Conclusion:

CSO:
Assigned:
Completed:
CSO Review Status:
To District-Final:
Rec'd District-Final:

Status/Date: CM COMPLETE 14-MAY-1996

CTRL H = Previous Block; CTRL N = Next Block; F4 = Exit;
Press RETURN to go to the Comment field.
Count: *1

<Replace>

EER Inspection For EER ID: 10038 & EER Type/#: N 020687

Facility: 42300 ROUSSEL UCLAF
ddress: 30721
ROMAINVILLE, FR

District:
Profile: TCM TABLETS, PROMPT RELEASE
Comment: MFG; NME PRODUCT
CFN: 9610109 DMF #: Insp ID: 24570 Fac. Type: FOR

Inspection Source: FF FOR FILE
Inspection Request Date:
Inspection Date: 15-APR-1996
Inspection Received:
CES Conclusion:

CSO:
Assigned:
Completed:
CSO Review Status:
To District-Final:
Rec'd District-Final:

Status/Date: CM COMPLETE 14-MAY-1996

CTRL H = Previous Block; CTRL N = Next Block; F4 = Exit;
Press RETURN to go to the Comment field.
Count: *1

<Replace>

*****EER Information******

EER ID: 10038 Division: 510 METABOLISM AND ENDOCRI
EER Type/#: N 020687 Requestor:
R Date: 17-APR-1996 Phone:
rofile: TCM TABLETS, PROMPT RELEASE Special Rev: 1 NEW MOLECULAR ENTITY

Appl Type/#: N 020687 Doc Type/#: N 000

Brand Name: Priority: 1S
Estab. Name: MIFEPRISTONE TABLETS
Dosage Form: TAB Strength: 200 MG
Applicant: POPULATION COUNCIL Sterility: NS
Address: 1230 YORK AVE
NEW YORK NY 10021 US

Received Date: 22-APR-1996
EER Technician:
EER CSO:
CES Supervisor:
EER Status/Date: CM COMPLETED 15-MAY-1996
CTRL H = Previous Block; CTRL N = Next Block; F4 = Exit

Count: *1 <Replace>

APPEARS THIS WAY
ON ORIGINAL

/S/
JAN 11 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: January 4, 2000	DUE DATE: January 13, 2000	OPDRA CONSULT #: 99-085

TO (Division): [redacted] Division of Reproductive and Urologic Drug Products (HFD-580)

PRODUCT NAMES: Mifeprex (mifepristone tablets) Alternate name [redacted] NDA: 20-687	**MANUFACTURER:** Population Council

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to a November 10, 1999 request by the Division of Reproductive and Urologic Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, Mifeprex, and the alternative name, [redacted] with other approved proprietary/generic names. This review includes studies conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name and the alternative name.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name, Mifeprex. However, OPDRA does not object to the use of the alternative proprietary name, [redacted] See review for details.

/S/

Office of Post-Marketing Drug Risk Assessment

/S/

Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; [redacted]
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: January 4, 2000

NDA: 20-687

NAME OF DRUG: Mifeprex (mifepristone tablets)
Alternate name - [redacted]

NDA HOLDER: Population Council

I. INTRODUCTION

This consult is in response to a request sent on November 10, 1999, from the Division of Reproductive and Urologic Drug Products, to review a proposed proprietary drug name, Mifeprex, and an alternate name [redacted] regarding potential name confusion with other proprietary/generic drug names. Container labels and carton labeling were not available for review of possible interventions in minimizing medication errors.

According to the Labeling and Nomenclature Committee (LNC) database, the proposed proprietary name, Mifeprex, was previously reviewed and was found to be unacceptable because of the look-alike and sound-alike similarity with Mirapex. The alternative name, [redacted] was found to be acceptable.

However, according to the Division, the proposed name, Mifeprex, was previously determined by the LNC to be unacceptable because the trademark contained the first part of the established name. The sponsor wishes to have the name reconsidered.

PRODUCT INFORMATION
Mifeprex (mifepristone) is a synthetic steroid with antiprogestational effects. The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Mifepristone has been shown to antagonize the endometrial and myometrial effects of progesterone in women. Furthermore, it also exhibits antiglucocorticoid and weak antiandrogenic activity. Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. If treatment fails to terminate a woman's pregnancy, fetal malformation may result, and pregnancy termination by surgery must be recommended. Following oral administration, mifepristone is rapidly absorbed with the peak plasma concentration occurring approximately 90 minutes after ingestion. The metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. Mifeprex is excreted in feces and urine. There are no data with respect to the

effects of mifepreprístone on hepatically and renally impaired patients. Mifeprex is supplied as 200 mg tablets. Detailed dosing guidelines are listed in the package insert.

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, Mifeprex, and the alternative name, [redacted] with other drug names, the medication error staff of OPDRA searched the MICROMEDEX Healthcare Intranet Series (1999), which includes the following: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, and Index Nominum. Other references include American Drug Index (43rd Edition), Drug Facts and Comparisons (Monthly Updates), PDR (53rd Edition, 1999), Electronic Orange Book, US Patent and Trademark Office online database, Drug Product Reference File (DPRF), Decision Support System (DSS), EES (Established Evaluation System), United States Adopted Names Council handbook (USAN 5th edition), and the LNC database for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted studies of written and verbal analyses of the proposed proprietary name and the alternative name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. Studies conducted within FDA

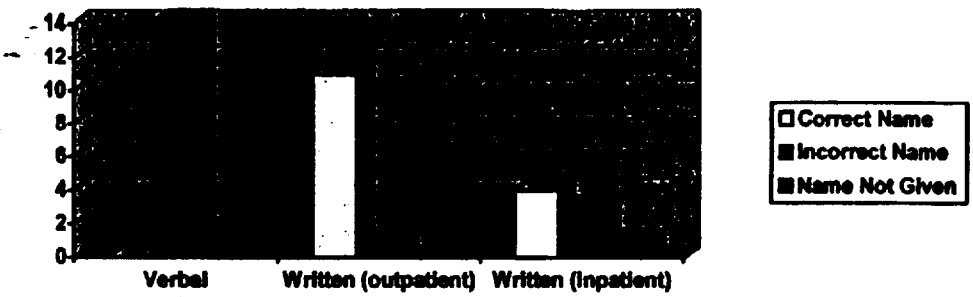
1) Methodology

One study involved forty-seven health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Mifeprex with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Forty-six health professionals were involved in the alternative name study. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff.

2) Results for Mifeprex

Sixteen inpatient written orders, fifteen outpatient written orders, and sixteen verbal orders sent to the study participants for the proposed proprietary name. We received responses from thirty-four participants. Twelve interpretations of outpatient written orders, fourteen interpretations of verbal orders, and eight interpretations of inpatient written orders were received for Mifeprex. Fifteen (out of thirty-four) participants interpreted Mifeprex correctly. The results are as follows:

Mifeprex



3) Results for

B. Focus Group Findings

1) The proposed proprietary name, Mifeprex, is similar to Mirapex and Niferex and may cause name confusion. In fact, one of the participants of the above study stated that Niferex came to mind when interpreting the written prescription for Mifeprex. Although the usual doses and dosage intervals are different for these two drugs, look-alike and sound-alike similarity alone could cause name confusion. Furthermore, these three drugs are available as tablet formulations. Moreover, medication errors involving these three drugs can be significant because of their different indications for use. Mifeprex is indicated for the termination of intrauterine pregnancy, Niferex is indicated for treatment of uncomplicated iron deficiency anemias, and Mirapex is indicated for signs and symptoms of idiopathic Parkinson's disease. Misadventures or substitution of any of these drugs for one another can have significant outcomes, including bleeding, unwanted abortion, asthenia, dystonia, postural hypotension, and worsening of Parkinson's disease or iron deficiency anemia.

   Although Niferex is an over-the-counter (OTC) drug, Niferex –PN, and Niferex-PN Forte are available as prescription drugs. Since these drugs are usually prescribed by number of tablets and not by a specific strength, the abbreviation, PN, when scripted, could be misconstrued as a numerical strength. Mirapex and Mifeprex are prescription drugs.

2) Examples of abortifacients include carboprost tromethamine and dinoprostone. Since Mifepristone is an another agent used for termination of pregnancy, the intention may have been to designate an established name that is similar to other abortifacients, with similar endings. However, the established name, mifepristone, look-alike and sound-alike misoprostol. In addition, these two drugs have the same numerical strength (mifepristone-200 mg, misoprostol-200ug). Although the units are different between the two drugs, the similarity in numerical strength could cause confusion and medication errors. These two drugs are also available as tablets. Moreover, these two prescription drugs may be stored in close proximity to each other, making it possible for dispensing errors to occur. Furthermore, according to the package insert for mifepristone, misoprostol is also indicated for a patient who is prescribed mifepristone, unless abortion has occurred and has been confirmed by clinical examination. Since these drugs should be taken in a specific order within 3 days of each other, a dispensing error of these drugs could cause preventable complications in terminating the pregnancy. *Since this issue involves name confusion between two established names, the USAN council should be contacted to verify the risk assessment of the established name, mifepristone, to be in accordance with 21 CFR 201.10 (c)(5).*

   One of the participants in the above study interpreted Mifeprex as Misoprostol even without knowing the established name of the product. Although the similarity between the proposed proprietary name and Misoprostol is not as evident as the above mentioned drugs in section B(1), this finding is still an

important consideration.

C. Discussion

The results of the written and verbal analyses demonstrate that only fifteen (out of thirty-four) participants interpreted Mifeprex correctly. One participant confused Mifeprex for Niferex, and another participant confused Mifeprex for Misoprostol. These findings are important given the small sample sizes of the studies and confirm the concerns expressed by the focus group regarding the name confusion between Mifeprex and existing approved drug names. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the names. However, in this case, the results of the Mifeprex study in combination with the possibilities of name confusion and the associated risks of medication errors are significant to render the proprietary name, Mifeprex, objectionable. Moreover, the analyses also demonstrate that the majority of the participants (twenty-one out of thirty-two) interpreted the alternative name, [redacted] incorrectly. Furthermore, [redacted] was confused for [redacted] However, there is insufficient evidence at this time to render the alternative name, [redacted] objectionable.

III. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name, Mifeprex.

B. OPDRA does not object to the use of the alternative proprietary name, [redacted]

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact [redacted]

/S/ 9/11/2000

[redacted]

Office of Post-Marketing Drug Risk Assessment

Concur:

[redacted]

Office of Post-Marketing Drug Risk Assessment

CC: NDA# 20-687
HFD-580; DivFiles; [redacted] Project Manager, DRUDP
HFD-580; [redacted]
Office Files
HFD-400; [redacted] OPDRA
HFD-400; [redacted] OPDRA
HFD-400; [redacted] OPDRA
HFD-2 ; [redacted] OPDRA

APPEARS THIS WAY
ON ORIGINAL

Memorandum

FEB 15 2000

To: NDA 20-687, Mifepristone Tablets, 200 mg

Addendum to Chemistry Review #4.

Through: /S/ 2/14/00

From: /S/ 2/15/00

Date: February 15, 2000

Re: Establishment Evaluation Request

Following re-inspection of the [redacted] on February 11, 2000, the District issued an acceptable recommendation. **However, the overall recommendation by the Office of Compliance is withhold (see attached EER).**

cc:
Orig. NDA #20-687
HFD-580 [redacted]
HFD-580 [redacted]
HFD-580 [redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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

Dear Dr. Mishell:

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

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

We appreciate the cooperation shown [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 yours,

[redacted]

151

[redacted]

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

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 2, 2000

TO: [redacted] Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: [redacted] HFD-45
Division of Scientific Investigations

FROM: [redacted]
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-687

APPLICANT: Population Council

DRUG: Mifepristone

THERAPEUTIC CLASSIFICATION: (1) Priority Review

INDICATION: Contraception

REVIEW DIVISION GOAL DATE: January 7, 2000
ACTION GOAL DATE (PDUFA Date): February 19, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this NDA submission is contraception.

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Daniel Mishell, M.D.	Los Angeles, CA	10/1/99	2/1/00	NAI/00076
Suzanne Poppema, M.D.	Seattle, WA	10/1/99	12/28/99	NAI/09946
Susan Haskell, M.D.	Des Moines, IA	10/1/99	11/29/99	NAI/09917

Site #1
Susan Haskell, M.D.
Planned Parenthood of Greater Iowa
851 19th Street
Des Moines, Iowa 50314
Acceptable

a. The field investigator reviewed 118 records from a total of 236.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

Site #2
Suzane T. Poppema, M.D.
Aurora Medical Services
1207 North Street, Suite 214
Seattle, WA 98133
Acceptable

a. The field investigator inspected portions of the study-related records for 65 of the 164 subjects enrolled in protocol #166 A at Dr. Poppema's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

Site #3
Daniel R. Mishell, Jr., M.D.
LAC/USC Medical Center
1240 North Mission Road
Room 2K1
Los Angeles, CA 90033
Acceptable

a. The field investigator inspected the study-related records for 15 of the 204 subjects enrolled in protocol #166 A at Dr. Mishell's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, no violations were observed that would affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed

[redacted] 2/2/00

DSI/GCPBI

CONCURRENCE:

[redacted]

Division of Scientific Investigations

APPEARS THIS WAY
ON ORIGINAL

FEB 16 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 16, 2000

FROM: [redacted] /S/ 2/16/00.
Concur. /S/ 2/16/00

Office of Clinical Pharmacology and Biopharmaceutics

SUBJECT: NDA 20-687

TO: File

The dissolution method and specification have been addressed by the Clinical Pharmacology and Biopharmaceutics review team and has been addressed in the Chemistry Review #4. The information conveyed is as follows:

Dissolution method and Specifications
Apparatus: USP 2 (paddle)
Medium: 0.01 N Hydrochloric acid
Speed: 50 RPM
Volume: 900 ml
Temperature: 37°C
Specification: Q=[redacted] min

APPEARS THIS WAY
ON ORIGINAL

SEP 14 2000

[redacted] **Memorandum**

Subject: Complete response dated March 31, 2000
to approvable action on Feb. 18, 2000
Received: NDA: 20-687
Date of Memorandum: 9/14/00
Indication: Medical termination of intrauterine pregnancy through 49 days of pregnancy
Drug: Mifepristone
Pharmacologic Class: Antiprogestational Agent
Dose: Three 200 mg tablets of mifepristone orally.
If termination of pregnancy has not occurred by day three, two 200 μg tablets of misoprostol are administered.
Sponsor: Population Council

Background

Mifepristone is a synthetic steroid that competitively inhibits the activity of progesterone. When it is used in combination with misoprostol, a prostaglandin analog, it results in termination of pregnancy.

The initial NDA was submitted on March 18,1996 and was granted priority review status. The sponsor submitted data from two trials completed in France and preliminary data from a large US study. In July 1996, The Reproductive Health Drugs Advisory Committee met to discuss the application. The Advisory Committee voted for approval with major recommendations regarding labeling, phase 4 commitments and restricted distribution. FDA agreed with the recommendations of the Advisory Committee and issued an approvable letter on Sept. 18, 1996, which specified the requirements for approval. Besides the clinical issues, there were significant chemistry and manufacturing deficiencies, which had to be addressed.

The response to the approvable letter was submitted by the sponsor on August 18, 1999 and included the final results of the US study. In this study of the 859 subjects with less than 49 days of amenorrhea, 92% had successful termination of pregnancy. There was a lower rate of efficacy beyond 49 days. The Division concluded that the drug regimen including mifepristone and misoprostol is safe and effective until 49 days of pregnancy as dated from the first day of the last menstrual cycle in a presumed 28-day cycle. However, CMC issues were not resolved and the drug substance manufacturing site failed inspection. During this review, The Division determined that 21 CFR 314.520 Subpart H applies to this application and that the drug can only be used safely with restricted distribution. On February 18, 2000, a second approvable letter was issued stating the issues that had to be addressed prior to approval. The major outstanding issues related to approvability of this drug are summarized as follows:

CMC issues related to drug substance, drug product and requirement for acceptable GMP inspection.

Phase 4 commitments

1. Monitor the adequacy of the distribution and credentialing system;

2. Follow the outcome of a representative sample of women who have surgical abortion because of method failure;

3. Access the long term effects of multiple uses of the regimen;

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

5. Study the safety and efficacy of the regimen in women under 18, over 35 and those who smoke; and

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

Acceptable Distribution Plan under 21 CFR 314.520 Subpart H

The Agency determined that the termination of an unwanted pregnancy is a "serious" condition under Subpart H and that that there is "meaningful therapeutic benefit" over existing surgical abortion because there is avoidance of a surgical procedure. In addition, the Agency has concluded that this product can only be used safely if the distribution is "restricted to certain facilities or physicians with special training or experience"

In the case of mifepristone, the Agency has determined that distribution should be limited to physicians who can date the pregnancy and diagnose ectopic pregnancies. These physicians need not have the skills for handling surgical intervention as long as they can provide appropriate referral services.

Labeling

The Label (package insert), Physician Agreement, Order Form, Patient Agreement and the Medication Guide are to be designed to educate the patient and physician regarding the mifepristone regimen. In addition, certain procedures and issues must be addressed that will reduce patient risk. These issues are:

The patients should have clear access to medical care should a surgical abortion be required or complication occur. The dispensing physician can provide these services or the patient can be referred to these services. However, in either case instruction should be given to the patient about what to do in the event of an emergency following administration of mifepristone.

The patient should return to the clinic on day 3 to receive misoprostol. Although there is some controversy about the need for a return visit, this reviewer believes that the additional contact with the health care provider would be useful for ongoing patient care, patient reassurance and reinforcement regarding the need to also return on day 14 for assessment of the success of the medication. The length of the day 3 visit can be a discussed between the patient and health care provider.

Division's Current Reviews Assessing Approvabilty of NDA 20-687

Chemistry/Manufacturing/Controls Review

In May 2000, the sponsor submitted new analytic, physical, and stability data, which were reviewed and found to be adequate to assure the quality of drug manufacturing. An inspection of the bulk drug substance maker was performed on July 24-28, 2000 in which deficiencies were cited. These were corrected and the corrections were found to be acceptable. The tradename, Mifeprex, is found to be acceptable.

Information in the appropriate sections of the label were found to be adequate

Pharmacology/Toxicology Review

Table 2, which describes on-going pregnancies after mifepristone treatment, not terminated by surgery, was updated. There are no additional cases of congenital malformations. There is insufficient evidence for the Agency to conclude that there is a causal relationship between use of mifepristone alone or in combination with a prostaglandin and fetal malformation. However, information that fetal malformation is a possible risk is included in the physician's and patient's educational material.

Information in the appropriate sections of the label were reviewed and found to be adequate.

Biopharmaceutics Review

The major focus during the current review cycle was the potential for drug interactions with and by mifepristone because CYP 3A4 is involved in its metabolism. Drugs are mentioned in the label that might inhibit or induce the metabolism of mifepristone.

In addition, coadministration of mifepristone may lead to an increase in serum levels of drugs that are substrates for CYP 3A4. Since mifepristone is slowly eliminated (half-life of 12 to 72 hours), an interaction could occur for a prolonged period of time after administration. This may become clinically important since some anesthetic drugs are metabolized by CYP 3A4 and a small proportion of mifepristone patients will require surgery and anesthesia.

The above, as well as other information in the appropriate sections of the label were reviewed and found to be adequate.

Clinical Review

The primary medical officer, who has reviewed the sponsor's application each time, again recommended approval of the application from a clinical standpoint. The medical officer reviewed the labeling and associated material and found them to be appropriate.

In addition, the medical officer reviewed Safety Update No. 3 and found that the "Safety
Update Report is consistent with the cumulative experience gained to date and does not reveal any unexpected, unanticipated safety issues that would change the benefit to risk ratio."

[redacted] **Assessment**

The clinical, pharmacology/toxicology, biopharmaceutics, and chemistry reviews were assessed. All recommended approval as previous deficiencies were satisfactorily addressed.

The six phase 4 commitments (see **Background**) communicated to the sponsor in the September 1996 letter, will be addressed by a program that includes two post-marketing studies. The first is a cohort-based study on the safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. The second one is a surveillance study on outcomes of ongoing pregnancies. Study questions regarding age, smoking and day 14 follow-up will be incorporated into the cohort study as well an audit of signed Patient Agreement forms.

The Label (package insert), Physician Agreement and Order Form, Patient Agreement and Medication Guide were reviewed and found to satisfactorily address previous deficiencies.

[redacted] **Conclusion**

An approval action is recommended for NDA 20-687.

/S/

9/14/00

DRUDP/CDER/FDA

**APPEARS THIS WAY
ON ORIGINAL**

[redacted] Memo
New Drug Application

FEB 17 2000

NDA: 20-687

Sponsor: Population Council, Inc.

Drug: [Tradename] (mifepristone) 200mg tablet for oral administration

Indication: Termination of intrauterine pregnancy up to 49 days since Last Menstrual Period (LMP)

Date received: Original NDA: March 18, 1996
Approvable letter issued: September 18, 1996
Complete Response received: August 18, 1999

Date of Memo: February 17, 2000

In this complete response to the approvable letter issued in September 1996, the applicant has presented further information in support of the use of mifepristone for the termination of pregnancy from diagnosis and up to seven weeks (49 days) of amenorrhea. In this setting mifepristone is ingested orally as three 200mg tablets followed 48 hours later by two 200ug tablets of misoprostol.

Clinical/Statistical

Results from several studies to establish the safety and efficacy of mifepristone plus misoprostol were reviewed as a result of the application submitted March 18, 1996. The two "pivotal" trials, both conducted in France, included in this original application revealed a complete abortion rate of 95% (for intrauterine pregnancies ≤ 49 days since last menstrual period—LMP). Although preliminary results from a large US trial were submitted for review with the original 1996 application, the current resubmission contains the final study report for this US trial.

The trial results are extensively described and analyzed in the Medical Officer review. Of the 2,121 women enrolled in the US, 859 were in the ≤ 49 days amenorrhea group. Efficacy was 92% in this group. Effectiveness was less beyond 49 days of amenorrhea. The original French studies reported an average duration of bleeding of 9 days. For the US studies this average was 14 days. Adverse event reporting was higher in the US population as compared to the French results but remained acceptable. The most common adverse event reported was abdominal cramping—an expected outcome. In the ≤ 49 days amenorrhea group, excessive bleeding led to transfusion in one US patient and an additional 2 women were treated in the emergency setting for excessive bleeding. The MO review describes data in comparison to surgical abortion. ~~In the end~~, I agree with the MO conclusion that mifepristone plus misoprostol as described in the clinical studies is effective for termination of pregnancies up to 49 days since LMP and has an acceptable safety profile.

Clinical Audits

In 1996, two French sites were audited and found acceptable. For this review cycle, three US sites were selected by the review team and were audited by the Division of Scientific Investigations. All three (sites in California, Washington and Iowa) were found acceptable.

Clinical Pharmacology and Biopharmaceutics

The outstanding question of appropriate dissolution specifications has been considered. The chemists and the Office of Clinical Pharmacology and Biopharmaceutics have described revised specifications. These specifications will be conveyed in the action letter.

Pharmacology/Toxicology

Adequate non-human studies have been performed and found acceptable. Labeling comments will be included in the action letter.

Chemistry

Our September 18, 1996 requests that the sponsor apply to USAN for an established name. The March 1997 correspondence from the sponsor indicates that they did not understand this request as they refer to determining a "tradename" rather than applying for an established name. In a further correspondence dated June 25, 1999 the applicant has indicated that they have obtained approval of the USAN council for adoption of the name, mifepristone.

The proposed tradename "Mifeprex" was found to not be acceptable by the Office of Post-marketing Drug Risk Assessment. The alternative name proposed [redacted] was found to be acceptable at this time.

As the chemistry reviews describe, several outstanding questions remain regarding both drug substance and drug product. Also, the drug substance manufacturing site has failed GMP inspection. Resolution of the chemistry and inspection issues will be required prior to an approval action.

Advisory Committee Activities

The Reproductive Health Drugs Advisory Committee met in July 1996 to consider this application and recommended approval. The committee expressed interest in seeing the final US study report as well as final labeling. The US study results, as published in an April 30, 1998 issue of the New England Journal of Medicine, were sent to the members of the Advisory Committee on November 1, 1999. No specific comments were received from this mailing.

Final labeling will be sent to the Advisory Committe members on approval of this application.

Labeling—prescription and patient

Our September 18, 1996 approvable letter requires submission of revised labeling. The sponsor has responded to these labeling requests in correspondence dated March 28, 1998 and again on June 25, 1999. The review team, along with the Division of Drug Marketing, Advertising and Communication have addressed the proposed labeling during this review cycle. All team comments have been collated and discussed. Our recommendations for labeling changes are provided in a "strike-out/underline" version and will be conveyed with the action letter. Major areas for consideration include:

1. We recommend that the labeling include a black boxed warning describing the major requirements and conditions for use.
2. The sponsor has proposed that the medication given on day 2 of the regimen (misoprostol) could be given either in the office/clinic (as per the clinical trials) or at home. The Division and Office have

discussed this proposal and find it acceptable. No changes in safety or efficacy are expected based on the location of ingestion of the misoprostol.

3. DDMAC has provided extensive comments regarding the patient labeling including the proposed "acknowledgement" section.

Distribution System and Subpart H recommendations

Under 21CFR 314 Subpart H, the agency can determine that a drug can be approved with restrictions to assure safe use. We have concluded that mifepristone is a candidate for Subpart H 314.520 when and if the product is approved. 314.520 states:

a If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
   1 Distribution restricted to certain facilities or physicians with special training or experience; or
   2 Distribution conditioned on the performance of specified medical procedures.

b The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

The sponsor submitted a distribution plan proposal in January 2000. After consideration of their proposal, we have concluded that the Subpart H provisions are appropriate for approval of this product. The distribution plan will need to be revised to include adequate training and certification of providers. The labeling and training materials will need to include information on reporting of events to both the sponsor and to the FDA. The distribution system will need to include a quality assurance/quality control component. As the system is developed, we can work with the applicant in order to incorporate a data collection component for the various Phase 4 commitments listed below.

Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.

Phase 4 Commitments

The approvable letter of September 1996 describes six areas of commitment made by the applicant for Phase 4 study. In this complete response of August 1999, the applicant addresses each commitment and proposes approaches to each of the commitments made. These commitments will again need to be included in the current action letter. The commitments include:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (a) less than 18 years of age, (b) over age 35 and (c) who smoke.
6. To ascertain the effect of the regimen on children born after treatment failure.

Other Petitions/Correspondence

A letter dated June 21, 1999 was sent to [redacted] Center for Drug Evaluation and Research (CDER), requesting a discussion of [redacted] issues for the drug substance

and product manufacturers. This letter was followed by a July 14, 1999 correspondence addressed to Office of Training and Communication (OTCOM), providing further discussion of the A subsequent correspondence was received in January, 2000.

Recommendations

Approval of this regimen is recommended once chemistry issues are adequately resolved and appropriate labeling and distribution system is in place.

/S/ 2/17/00

Division of Reproductive and Urologic Drug Products

cc: NDA 20-687
HFD-580
HFD-103

APPEARS THIS WAY
ON ORIGINAL

FEB 15 2000

Addendum to the Summary of Chemistry Review of NDA 20-687

A. Drug Product:

On February 14, 2000, the Office of Compliance has made a recommendation of "Acceptable" for the [redacted]

/S/ 2/15/00

[redacted]

Division of Reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

cc: original NDA 20-687
HFD-580
HFD-580/[redacted]
HFD-820/[redacted]

APPEARS THIS WAY
ON ORIGINAL

SEP 17 1996

[redacted] MEMO TO FILE

Date: September 17, 1996

NDA: 20-687

Product: Mifepristone

Sponsor: Population Council

Submission date: March 16, 1996, Received: March 18, 1996

****

The review team has worked hard on this priority application and I agree with the recommendation that the application is approvable.

Chemistry and biopharmaceutics deficiencies, discipline-specific labeling modifications and Phase 4 agreements have been conveyed to the sponsor and are reiterated in the letter being forwarded to [redacted] for consideration.

[redacted] Group Leader memorandum reviews several outstanding clinical issues which have been discussed with and will continue to be addressed by the sponsor.

Along with the specific items enumerated in the action letter, the sponsor is aware that further items/modifications will require consideration before an approval action would be recommended. These include:

1. Continued update of data from the US clinical trial of this regimen.

2. Appropriate labeling

Along with the modifications suggested in the action letter, we must also consider appropriate changes to the patient labeling once the prescribing information is adequately revised. We also have asked the Division of Drug Marketing, Advertising and Communications to comment on the acceptability of the patient information and will incorporate their comments as labeling discussions continue.

3. Drug Distribution System

I agree with [redacted] conclusion that, if the applicant's proposal for a voluntarily system of limited distribution appears adequate, the imposition of further restrictions would not be warranted. We look forward to receiving a more comprehensive description of the proposed distribution system prior to a final determination on this issue.

4. Phase 4 agreements

As in our letter of August 22nd, with several modifications after discussion with the sponsor on September 12th, the six areas of post-approval monitoring as described in the forwarded action letter have been considered and will be pursued by the applicant after an approval action (as confirmed by a September 16th telefacsimile from the Population Council).

5. Advisory Committee input

Finally, the Reproductive Health Drugs Advisory Committee, which considered this application at a July 19, 1996 meeting, hopes to have the opportunity to comment on modified proposed labeling before approval as well as have the ability to review the final US study results when submitted and we anticipate providing this information as available.

In conclusion, I concur with the review team that an "approvable" letter be communicated to the sponsor at this time for mifepristone 600 mg, followed by 400ug of misoprostol two days later (unless termination has occurred) for pregnancy termination in women whose duration of amenorrhea is no more than 49 days. As agreed by the sponsor, the Center for Drug Evaluation and Research and the Reproductive Health Drugs Advisory Committee, the safe and effective use of this regimen requires certain conditions of use as described in the labeling.

/S/

7-96

Division of Reproductive and Urologic Drug Products
HFD-580

cc:
NDA 20-687
HFD-580

[redacted]

Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). This notice also summarizes the procedures for the meeting and methods by which interested persons may participate in open public hearings before FDA's advisory committees.

FDA has established an Advisory Committee Information Hotline (the hotline) using a voice-mail telephone system. The hotline provides the public with access to the most current information on FDA advisory committee meetings. The advisory committee hotline, which will disseminate current information and information updates, can be accessed by dialing 1–800–741–8138 or 301–443–0572. Each advisory committee is assigned a 5-digit number. This 5-digit number will appear in each individual notice of meeting. The hotline will enable the public to obtain information about a particular advisory committee by using the committee's 5-digit number. Information in the hotline is preliminary and may change before a meeting is actually held. The hotline will be updated when such changes are made.

MEETING: The following advisory committee meeting is announced:

Advisory Committee for Reproductive Health Drugs

Date, time, and place. July 19, 1996, 9 a.m., FDA Technical Center, 16071 Industrial Dr., Gaithersburg, MD. Attendees should allow time to proceed through security procedures. Admission to the facility by public participants will be available on a first come, first serve basis, and will be limited to approximately 200, the number of seats available to the public in the conference room. There will be an overflow room with both audio and video link to the meeting. The overflow room is located at the Hilton Hotel, 620 Perry Pkwy., Gaithersburg, MD.

Type of meeting and contact person. Open committee discussion, 9 a.m. to 1:30 p.m.; open public hearing, 1:30 p.m. to 3:30 p.m., unless public participation does not last that long; open committee discussion, 3:30 p.m. to 5 p.m.; Philip A. Corfman, Center for Drug Evaluation and Research (HFD–580), Food and Drug Administration, 5600 Fishers Lane, rm. 14B–04, Rockville, MD 20857, 301–443–3510, FAX 301–443–6282, or e-mail july19@cder.fda.gov. Information concerning the meeting is available from FDA Advisory Committee Information Hotline, 1–800–741–8138 (301–443–0572 in the Washington, DC area), Advisory Committee for Reproductive Health Drugs, code 12537. Please call the hotline for information concerning any possible changes.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational human drugs for use in the practice of obstetrics, gynecology, and related specialties.

Agenda—Open public hearing. Interested persons may present data, information, or views, orally or in

writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person in writing by mail, e-mail, or fax no later than 5 p.m., EDT on July 12, 1996, with a brief statement of the general nature of the evidence or arguments they wish to present, the names, telephone numbers, and addresses of proposed participants, and an indication of the approximate time required to make their comments. The time for presentations will be allotted equitably, and will depend on how many individuals give advance notice within the time indicated of their intention to speak. In the interest of time, the agency may require persons with common interests to make joint presentations.

Open committee discussion. The committee will discuss the new drug application for mifepristone for the interruption of early pregnancy.

FDA public advisory committee meetings may have as many as four separable portions: (1) An open public hearing, (2) an open committee discussion, (3) a closed presentation of data, and (4) a closed committee deliberation. Every advisory committee meeting shall have an open public hearing portion. Whether or not it also includes any of the other three portions will depend upon the specific meeting involved. There are no closed portions for the meetings announced in this notice. The dates and times reserved for the open portions of each committee meeting are listed above.

The open public hearing portion of each meeting shall be at least 1 hour long unless public participation does not last that long. It is emphasized, however, that the 1 hour time limit for an open public hearing represents a minimum rather than a maximum time for public participation, and an open public hearing may last for whatever longer period the committee chairperson determines will facilitate the committee's work.

Public hearings are subject to FDA's guideline (subpart C of 21 CFR part 10) concerning the policy and procedures for electronic media coverage of FDA's public administrative proceedings, including hearings before public advisory committees under 21 CFR part 14. Under 21 CFR 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants.

Meetings of advisory committees shall be conducted, insofar as is practical, in accordance with the agenda published in this Federal Register notice. Changes in the agenda will be announced at the beginning of the open portion of a meeting.

Any interested person who wishes to be assured of the right to make an oral presentation at the open public hearing portion of a meeting shall inform the contact person listed above in writing prior to the meeting.

The agenda, the questions to be addressed by the committee, and a current list of committee members will be available at the meeting location on the day of the meeting.

Transcripts of the open portion of the meeting may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857, approximately 15 working days after the meeting, at a cost of 10 cents per page. The transcript may be viewed at the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, approximately 15 working days after the meeting, between the hours of 9 a.m. and 4 p.m., Monday through Friday. Summary minutes of the open portion of the meeting may be requested in writing from the Freedom of Information Office (address above) beginning approximately 90 days after the meeting.

This notice is issued under section 10(a)(1) and (2) of the Federal Advisory Committee Act (5 U.S.C. app. 2), and FDA's regulations (21 CFR part 14) on advisory committees.

Dated: June 25, 1996.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 96-16770 Filed 6-28-96; 8:45 am]

BILLING CODE 4160-01-F

Reproductive Health Drugs Advisory Committee

FDA Technical Center
Gaithersburg MD
19 July 1996

AGENDA

0900-0905 Opening comments. Confirmation of subsequent meeting dates: 20-22 November 1996; 13-14 February 1997; 5-6 June 1997.

NEW DRUG APPLICATION (NDA) FOR THE USE OF MIFEPRISTONE FOR INTERRUPTION OF EARLY PREGNANCY

0905-0915 Opening comments
David A. Kessler, MD
Commissioner of Food and Drugs

0915-1200 Presentations by the Sponsor, The Population Council (PC)

Sandra P. Arnold, BA (Mathematics)
Vice-President, Corporate Affairs (PC)

Ann Robbins, PhD
Scientist, Center for Biomedical Research (PC)

Irvin M. Spitz, MD
Senior Scientist, Center for Biomedical Research (PC)

C. Wayne Bardin, MD
Independent Consultant

Beverly Winikoff, MD, MPH
Program Director
Reproductive Health Programs Division (PC)

Elizabeth Newhall, MD
Medical Director, Downtown Women's Center
Portland, Oregon

1200-1300 Presentations by the FDA Reviewing Division

Introduction
Lisa Rarick, MD
Acting Director, Division of
Reproductive and Urologic Drug Products

Review of pharmacology and toxicology findings
Alexander Jordan, PhD
Pharmacology Team Leader

Review of non-US clinical findings
Ridgely C. Bennett, MD, MPH
Medical Officer

Review of US clinical findings and considerations for use
Lisa Rarick, MD

1300-1400 Lunch

1400-1630 Open Public Hearing

Private citizens or representatives of the following organizations (except for Congressman Coburn's office) contacted the Agency before 5 pm EDT on 12 July to request time to speak:

1. Office of Congressman Tom Coburn
   Member, United States House of Representatives
   Michael Schwartz
2. Alan Guttmacher Institute
   Lisa Kaeser, JD
3. American College of Obstetricians and Gynecologists
   Carolyn L. Westoff, MD
4. American Life League, Inc.
   Rebecca Lindstedt
5. American Medical Student Association
   Paul Jung, MD
6. American Medical Women's Association
   Diana Dell, MD
7. American Public Health Association
   Allan Rosenfield, MD
8. American Victims of Abortion
   Olivia L. Gans
9. Baruch College
   Joel Brind, PhD
10. Private citizen
    Randy O'Bannon, speaking for Charles Cargille, MD
11. Center for Reproductive Law and Policy
    Janet Benshoof, JD
12. Private citizen
    Helen M. Donovan, JD
13. Family Research Council
    Gracie S. Hsu, MHS
14. Feminist Majority Foundation
    Eleanor Smeal
15. Feminist Women's Health Center
    Marie Head
16. Jones Institute for Reproductive Medicine
    Gary D. Hodgen, PhD
17. Life Issues Institute
    Richard D. Glasow, PhD
18. National Abortion and Reproductive Rights League
    Marcy J. Wilder, JD
19. National Abortion Federation
    Paul Blumenthal, MD

20. National Association of Nurse Practitioners in Reproductive Health
    Susan Wysocki, RNC, NP
21. National Council of Jewish Women
    Donna Gary
22. National Organization for Women, Inc.
    Janice E. Erickson
23. National Women's Health Network
    Cynthia A. Pearson
24. National Women's Health Organization
    Susan Hill
25. National Women's Law Center
    Ann Kolker
26. Northeast Waterloo Family Practice
    M. Louviere, MD
27. Pharmacists for Life, International
    Mary Jasinski Caldwell
28. Planned Parenthood Federation of America
    Gloria M. Feldt
29. Planned Parenthood of Westchester and Rockland, Inc.
    Lynn Borgatta, MD, MPH
30. Reproductive Health Technologies Project
    Marie Bass
31. Private citizen
    Wendy Simonds, PhD
32. Society of Physicians for Reproductive Choice and Health
    Seymour L. Romney, MD
33. Southwestern Medical Clinic, PC
    Donna J. Harrison, MD
34. Women's Legal Defense Fund
    Joanne L. Hustead

1630-1645 Break

1645-1845 Discussion and response to questions

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS
CENTER FOR DRUG EVALUATION AND RESEARCH

CHAIRMAN

Davidson, Jr., Ezra C., M.D. 6/30/97
Professor and Chair
Department of Obstetrics and Gynecology
Charles R. Drew University of Medicine
and Science
1621 E. 120th Street
Los Angeles, California 90059

EXECUTIVE SECRETARY

Corfman, Philip A., M.D.
Supervisory Medical Officer
for Fertility and Maternal
Health Drugs (HFD-510)
Food and Drug Administration
5600 Fishers Lane, Room 14B-04
Rockville, Maryland 20857
(301) 443-3510 Fax: (301) 443-9282

MEMBERS

Kosasa, Thomas S., M.D. 6/30/97
Associate Professor
Dept. of Obstetrics and Gynecology
John A. Burns School of Medicine
University of Hawaii
1319 Punahou Street, Suite 1040
Honolulu, Hawaii 96826

O'Sullivan, Mary Jo, M.D. 6/30/97
Professor and Director of Obstetrics
Department of Obstetrics and Gynecology
University of Miami School of Medicine
Jackson Memorial Hospital
1611 Northwest 12th Avenue
East Tower Building
4th Floor, Room 4070
Miami, Florida 33136

Ryan, Kenneth J., M.D. 6/30/97
Professor and Chairman
Brigham and Women's Hospital
Harvard Medical School
75 Francis Street
Boston, Massachusetts 02115

Lewis, Vivian, M.D. 6/30/98
Director
Division of Reproductive Endocrinology
University of Rochester Medical Center
601 Elmwood Avenue, Box 668
Rochester, New York 14642

Narrigan, Deborah L., M.S.N., C.N.M.
Course Coordinator 6/30/98
Frontier School of Midwifery
and Family Nursing
P.O. Box 528
Hyden, Kentucky 41749

Petitti, Diana B., M.D., M.P.H. 6/30/98
Director, Research and Evaluation
Kaiser Permanente Medical Care Program
Southern California Region
393 East Walnut Street
Pasadena, California 91188

Former committee members with terms ending 6/30/96 attending this meeting as Consultants:

Daling, Janet R., Ph.D. 6/30/96
Member
Fred Hutchinson Cancer Research Center
1124 Columbia Street (MET 381)
Seattle, Washington 98104

Henderson, Cassandra E., M.D. 6/30/96
Associate Professor
Department of Obstetrics and Gynecology
Albert Einstein College of Medicine
1825 Eastchester Road
Bronx, New York 10461

Consumer Representative:
Zones, Jane S., Ph.D. 6/30/96
Adjunct Assistant Professor
Dept. of Social and Behavioral Sciences
University of California, N631Y
San Francisco, California

FDA Guest Speaker:
Ricardo Azziz, M.D., M.P.H.
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
University of Alabama at Birmingham
Old Hillman Building 549
618 South 20th Street
Birmingham, Alabama 35233-7333

July 19, 1996

Reproductive Health Drugs Advisory Committee

FDA Technical Center
Gaithersburg MD
19 July 1996

QUESTIONS

The regimen proposed for the use of mifepristone for the termination of early pregnancy consists of the oral administration of 600 milligrams of mifepristone within 49 days after the beginning of the last menstrual period, followed by oral administration of 400 micrograms of misoprostol 48 hours later.

1. a. Do the results of the open-label, historically controlled studies conducted in France establish the efficacy of this regimen for use in the United States?
   b. If not, what additional efficacy information should the applicant provide?
2. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience.
   a. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication?
      In your discussion, please include comments on the following issues:
      - *Whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled.*
      - *The acceptability of the frequency of adverse events.*

   b. If not, what additional safety information should the applicant provide?
3. Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States?
4. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?
5. If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?
6. If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?
7. If the regimen were to be approved, what recommendations, if any, do you have for post-marketing studies?

Reproductive Health Drugs Advisory Committee

FDA Technical Center
Gaithersburg, Maryland
19 July 1996

MINUTES

Members Present	Members Absent
Ezra C. Davidson, Jr, MD (Chair)	Kenneth Ryan, MD
Janet R. Daling, PhD	Edward Wallach, MD
Cassandra E. Henderson, MD	
Thomas S. Kosasa, MD	
Vivian Lewis, MD	
Deborah L. Narrigan, MSN, CMN	
Mary Jo O'Sullivan, MD	
Diana B. Petitti, MD, MPH	
Jane S. Zones, PhD	

Invited Guests

Ricardo Azziz, MD

Executive Secretary

Philip A. Corfman, MD

"We certify that we attended the 19 July 1996 meeting of the Reproductive Health Drugs Advisory Committee and that these Summary Minutes accurately reflect what transpired."

Philip A. Corfman, MD
Executive Secretary
22 July 1996
Date

Ezra C. Davidson, MD
Chair
July 23, 1996
Date

The Reproductive Health Drugs Advisory Committee of the Food and Drug Administration met on 19 July 1996 at the Food and Drug Adminstration's Technical Center in Gaithersburg, Maryland. A complete transcript of the meeting is available from the Dockets Management Branch. The following documents are annexed to these Summary Minutes:

1. The Agenda.
2. Questions put to the Committee.
3. A list of Committee members and the Guest invited by the FDA.

The meeting was opened by the Chair with comments concerning the exemplary service of the members whose terms on the Committee have ended, Drs. Janet Daling, Cassandra Henderson, and Jane Zones, and greetings to the Invited Guest, Dr. Ricardo Azziz, who becomes a member of the Committee this year. The Chair also introduced Agency staff at the Committee table: Commissioner David Kessler, Deputy Commissioner Mary Pendergast, and Acting Director of the Reproductive and Urologic Drugs Advisory Committee, Dr. Lisa Rarick.

Subsequent committee meeting dates were confirmed as follows:
20-22 November 1996
13-14 February 1997
5-6 June 1997

Ms. Marina Hooten, the Chief of the Ethics Branch in the Agency's Division of Ethics and Program Integrity, read the Conflict of Interest statement, noting that, due to the possibly apparent conflict of interest, Dr. Zones, though permitted to participate fully in the proceedings, has been asked not to vote, if votes are to be taken.

The Chair then opened the meeting to the principal topic.

NEW DRUG APPLICATION FOR THE USE OF MIFEPRISTONE FOR INTERRUPTION OF EARLY PREGNANCY

After an introduction to the topic by Commissioner David Kessler, the sponsor, the Population Council, presented its findings and recommendations. Presentations were given by Ms. Sandra Arnold, Drs. Ann Robbins, Irvin Spitz, Wayne Bardin, Beverly Winikoff, and Elizabeth Newhall. During these presentations there was discussion of the issues with Committee members. Dr. Robbins concluded the sponsor's presentations.

The next major agenda item was presentations of the Agency's review of the Application by staff of the Reproductive and Urologic Drugs Products Division, including the Acting Director, Dr. Lisa Rarick, and Drs. Alexander Jordan and Ridgely Bennett. There was discussion of the issues with Committee members during and after these presentations.

The afternoon session began with the Open Public Session, with presentations by the following individuals, speaking either as private citizens or on behalf of the organizations they represented:

Office of Congressman Tom Coburn
Member, United States House of Representatives
Michael Schwartz

Alan Guttmacher Institute
Lisa Kaeser, JD

American College of Obstetricians and Gynecologists
Carolyn L. Westoff, MD

American Life League, Inc.
Rebecca Lindstedt

American Medical Student Association
Paul Jung, MD

American Medical Women's Association
Diana Dell, MD

American Public Health Association
Allan Rosenfield, MD

American Victims of Abortion
Olivia L. Gans

Baruch College
Joel Brind, PhD

Private citizen
Randy O'Bannon, speaking for Charles Cargille, MD

Center for Reproductive Law and Policy
Janet Benshoof, JD

Private citizen
Helen M. Donovan, JD

Family Research Council
Gracie S. Hsu, MHS

Feminist Majority Foundation
Eleanor Smeal

Feminist Women's Health Center
Marie Head

Life Issues Institute
Richard D. Glasow, PhD

National Abortion and Reproductive Rights League
Marcy J. Wilder, JD

National Abortion Federation
Paul Blumenthal, MD

National Association of Nurse Practitioners
in Reproductive Health
Susan Wysocki, RNC, NP

National Council of Jewish Women
Donna Gary

National Organization for Women, Inc.
Janice E. Erickson

National Women's Health Network
Cynthia A. Pearson

National Women's Health Organization
Susan Hill

National Women's Law Center
Ann Kolker

Northeast Waterloo Family Practice
M. Louviere, MD

Pharmacists for Life, International
Mary Jasinski Caldwell

Planned Parenthood Federation of America
Gloria M. Feldt

Planned Parenthood of Westchester and Rockland, Inc.
Lynn Borgatta, MD, MPH

Reproductive Health Technologies Project
Marie Bass

Private citizen
Wendy Simonds, PhD

Society of Physicians for
Reproductive Choice and Health
Seymour L. Romney, MD

Southwestern Medical Clinic, PC
Donna J. Harrison, MD

Women's Legal Defense Fund
Joanne L. Hustead

After completion of the Open Public Hearing, the Chair directed the attention of the Committee to the questions.

ANSWERS TO THE QUESTIONS

AGENCY STATEMENT INTRODUCING THE QUESTIONS
"The regimen proposed for the use of mifepristone for the termination of early pregnancy consists of the oral administration of 600 milligrams of mifepristone within 49 days after the beginning of the last menstrual period, followed by oral administration of 400 micrograms of misoprostol 48 hours later."
CHANGE IN STATEMENT
The Committee began its deliberations on the questions by changing the phrase "48 hours" to "2 days" in this statement.

QUESTION 1.

a. Do the results of the open-label, historically controlled studies conducted in France establish the efficacy of this regimen for use in the United States?
ANSWER
The Committee voted 6 in favor and 2 opposed in response to this question.

b. If not, what additional efficacy information should the applicant provide?
ANSWER
In response to this question, the Committee voted unanimously (8 to 0) in favor of the following motion:
"The Committee has some reservations about finally determining efficacy without access to the US data and recommends to the Agency that the Committee would like the opportunity to review the data when they are available."

QUESTION 2.
The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience.

a. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication?
In your discussion, please include comments on the following issues:
- o Whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled.
- o The acceptability of the frequency of adverse events.

ANSWER
The Committee voted 7 in favor and 1 in abstention in response to this question. (The Committee provided no specific responses to the two issues on this questions presented by the Agency.)

b. If not, what additional safety information should the applicant provide?
ANSWER
The Committee discussed the issue of safety at length and stated that it would like be to be informed of the final analysis of the safety data from the US studies.

QUESTION 3.
Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States?
ANSWER
The Committee voted 6 in favor and 2 in abstention in response to this question.

QUESTIONS 4 and 5.
4. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?
5. If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?
ANSWER
In response to Questions 4 and 5, the Committee made the following statement:
"With regards to labeling for both physicians and the patients, the Committee is concerned that the precautions and conditions employed in the clinical trials - such as under age 18, over age 35, smoking, and certain chronic medical conditions - be described in the labeling and noting that there are as yet no data concerning the safety of the use of the regimen by women with such conditions. The Committee also recommended that patient labeling include what is known about possible teratogenicity in humans, that the risk to fetuses of pregnancies that are not terminated by the regimen is not certain, but women should be offered surgical terminations when failures occur."

QUESTION 6.
If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?
ANSWER
The Committee voted unanimously (8 to 0) in favor of the following statement:
"We agree in concept with the proposal but have serious reservations on how it is currently described in terms of assuring safe and adequate credentialing of providers."

QUESTION 7.
If the regimen were to be approved, what recommendations, if any, do you have for post-marketing studies?
ANSWER
The Committee recommended that several issues be studied after the regimen is marketed including the following:

- *monitor the adequacy of the distribution and credentialing system by determining, among other end points, the frequency of post-surgical complications;*
- *follow-up on the outcome of all women who have surgical abortion because of method failure;*
- *studies of the long-term effects of multiple use of the regimen;*
- *ascertainment of the number of women who follow the complete regimen of treatment, and follow-up of women who do not;*
- *studies of the efficacy and safety of the regimen in women under age 18, over age 35, and in smokers; and*
- *ascertainment of the effect of the regimen on children born after treatment failure.*

The Committee having completed the agenda, the Chair closed the meeting.

EXCLUSIVITY SUMMARY FOR NDA # ___20-687_____ SUPPL #_____

Trade Name _Mifeprex_____ Generic Name _mifepristone___

Applicant Name _Population Council HFD # _580_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 [redacted]

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5-years

e) Has pediatric exclusivity been granted for this Active Moiety?

_____NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 9/15/00

Signature Date

Title:_____

/S/ 9/20/00

Signature of Office/ Date

cc: Original NDA Division File HFD-93 [redacted]

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

Searches
Pediatric Summary
Main Search

NDA Number: 020687 Trade Name: MIFEPRISTONE 200MG TABS
Supplement Number: 000 Generic Name: MIFEPRISTONE 200MG TABS
Supplement Type: N Dosage Form:
Regulatory Action: AP COMIS Indication: INDUCTION OF ABORTION
Action Date: 9-28-00

Indication # 1 Induction Abortion
Label Adequacy: Does Not Apply
Forumulation Needed: 0
Comments (if any): Safety and efficacy in patients less than 18 years of age have not been studied in the clinical trials. However, safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18. 9-28-00

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	9/28/00

Comments: Safety and efficacy in patients less than 18 years of age have not been studied in the clinical trials. However, safety and efficacy are expected to be the same for postpubertal adolescents under the age of 18. 9-28-00

This page was last edited on 9/28/00

/S/

Date 9/28/00

APPEARS THIS WAY
ON ORIGINAL

Mifepristone
NDA No. 20-687

GENERIC DRUG ENFORCEMENT ACT OF 1992
CERTIFICATION STATEMENT

The Population Council hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed: Sandra Arnold Date: 9/26/03

SANDRA ARNOLD, VICE PRESIDENT

The Population Council

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

~~NDA 20-687~~

Food and Drug Administration
Rockville MD 20857

INFORMATION REQUEST LETTER

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

SEP 13 2000

Dear Ms. Arnold:

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

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

We are reviewing your proposed Physician Package Insert, Patient Agreement and distribution system, Exhibit E of the Distribution Plan, (Prescriber's Agreement and Order Form) for this application. We are providing you with the attached draft Physician Package Insert, Patient Agreement and the revised Exhibit E of the Distribution Plan (Prescriber's Agreement and Order Form).

In addition, we have reviewed your proposed Phase 4 protocols submitted September 6, 2000, and we propose that you accept the revised Phase 4 protocols as presented in the following attachment.

Please review the attached documents and provide your prompt written response so that we can continue our evaluation of your NDA.

If you have any questions, please contact Regulatory Project Manager, at

/S/

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

Attachments: Physician Package Insert, Patient Agreement, Exhibit E of the Distribution Plan, (Prescriber's Agreement and Order Form), and Phase 4 Protocols

24 **Page(s) Redacted**

Draft

Labeling

/S/

NDA 20-687

INFORMATION REQUEST LETTER

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

AUG 30 2000

Dear Ms. Arnold:

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

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

We are reviewing your proposed patient labeling and distribution system, Exhibit E of the Distribution Plan, (Prescriber's Letter and Order Form) for this application. We are providing you with the attached draft Medication Guide, and with comments included in the revised Exhibit E of the Distribution Plan (Prescriber's Agreement and Order Form).

Please review the attached documents and provide your prompt written response so that we can continue our evaluation of your NDA.

If you have any questions, please contact , Regulatory Project Manager, at

Sincerely,

/S/

8/30/00

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

Attachments

APPEARS THIS WAY
ON ORIGINAL

8 Page(s) Redacted

Draft

Labeling

NDA 20-687

INFORMATION REQUEST LETTER

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

JUN 30 2000

Dear Ms. Arnold:

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

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

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

Physician Package Insert

Carcinogenesis, Mutagenesis, Impairment of Fertility

1 **Page(s) Redacted**

Draft

Labeling

Nursing Mothers

[redacted]

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

Sincerely,

/S/ 6/30/00

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

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-687
HFD-580/Div. Files
HFD-580/ [redacted]
HFD-580/ [redacted]
HFD-103 [redacted]
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: — June 30, 2000
Initialed by: [redacted] 6.30.00/ [redacted] 6.30.00/ [redacted] 6.30.00
final: [redacted] 6.30.00
filename: [redacted]

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-687

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

JUN 23 2000

Dear Ms. Arnold:

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

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

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

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

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

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

/S/ [redacted] 6/23/00

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

APPEARS THIS WAY
ON ORIGINAL

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

APR 25 2000

Dear Ms. Arnold:

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

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

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

If you have any questions, call [redacted] Regulatory Project Manager, at [redacted]

Sincerely,

/S/ 4/25/00

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

APPEARS THIS WAY
ON ORIGINAL

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 [redacted]

Sincerely yours,

/S/

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

/S/

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

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

Sincerely yours,

[redacted]

3-19-96

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

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

July 11, 2000

BY HAND

[redacted]

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

NEW CORRESP
NC

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

Dear [redacted]

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

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

cc: [redacted]

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

151 7/13/00
CSO INITIALS DATE

One Dag Hammarskjold Plaza, New York, New York 10017

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

June 23, 2000

VIA FEDERAL EXPRESS

[redacted]

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

NEW CORRESP.
NC

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

Dear [redacted]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We think the training materials and programs already or soon to be available are quite extensive in light of the relative simplicity of the mifepristone protocol, and we therefore believe they are more than adequate to achieve the goal of prescriber knowledge. [

]

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

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

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

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

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

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

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

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

Next, there is the question of whether the mifepristone prescriber must himself or herself be able to perform instrumental pregnancy termination using both vacuum aspiration and dilation and curettage (i.e., surgical abortion). We think such a requirement is wholly inappropriate. Specialization is a fact of life in modern American medical practice, and it is absolutely routine for physicians to refer patients to one or more other physicians for various aspects of their care. Such referrals can occur at any time in the clinical course of a disease or condition; they are sometimes made at the outset of a patient's care, sometimes during the course of a patient's care for a second opinion or more extensive involvement by another doctor, and sometimes on an emergent basis when the original provider needs help or the patient is away from the original provider's location. There is no reason at all for mifepristone to be one of the very few exceptions to these common practices, and there are at least two very important reasons for it not to be.

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

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

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

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

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

[redacted]

facility. As noted above, further care, if needed, will be provide
the prescriber need not be geographically proximate to any parti
necessary care.

In summary, we intend to carry out fully our commitmen
expert assistance to physicians who prescribe mifepristone, and w
commitments to provide, via their physicians, written information
abortion with mifepristone. We believe that with that information
available expert assistance, if needed, and in light of the safety anc
predictability of the course of patients who take it, physicians will
of patients who choose medical abortions with mifepristone. To re
unnecessary and therefore inappropriate, and also unfortunately lik
new drug.

* * *

FDA's minutes of our June 1 telephone call also discuss que
questions, such as Phase IV commitments, the applicability of Subpa
As to Phase IV, we reiterate our intention to submit proposed protoc
Subpart H, we continue to believe that it is impermissible for FDA to
because the drug is not intended for use in either serious or life-threat
to have use of this important drug discouraged by branding it as a Sub
previous comments on this issue is attached.

[redacted]

As to the labeling recommendations briefly noted in the minut
with you on revisions to simplify the labeling and make it more effecti
have received FDA's comments on and information requests about the
requested, respond promptly in writing.

APPEARS THIS
ON ORIGIN

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

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

* * *

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

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

Population Council

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

Very truly yours,

Sandra Arnold

Sandra P. Arnold

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

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

Frederick H. Schmidt – Population Council

Patricia Vaughan, Esq. – Population Council

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

Danco Laboratories, LLC

[redacted]

June 22, 2000

[redacted]

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

ORIG AMENDMENT

BX

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

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

Dear [redacted]

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

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

A. Validated Process Adjustments

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

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

These changes were initially developed and evaluated at laboratory scale (see Attachment A-3, Laboratory Scale Validation Protocol and Report) and were subsequently validated in a ten (10) batch plant scale manufacturing campaign, (see Attachment A-4, Plant Scale Validation Protocol and Report). The results of the process validation showed that the mifepristone manufacturing process performed consistently and within specification, and resulted in mifepristone that was comparable to the mifepristone produced during the initial validation campaign. Additionally, samples of mifepristone from the adjusted process were tested by [redacted] at a qualified laboratory in the United States and were confirmed as the intended [redacted] (See Attachment A-5). (Pursuant to discussions with [redacted] earlier this week, we will be following up in the near future with [redacted]

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

B. Other Corrections

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

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

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

Sincerely,

/S/

[redacted]

Enclosures

cc: Sandra P. Arnold – Population Council

[redacted]

Nancy L. Buc, Esq. – Buc & Beardsley

[redacted]

Frederick H. Schmidt – Population Council

Danco Laboratories, LLC [redacted]

May 17, 2000

[redacted] RIGINAL

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

ORIG AMENDMENT

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 047 - Additional Information on [redacted] Impurity Profile for Roussel Drug Product and Danco Stability Commitment

Dear [redacted]

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

1) The commitment to develop [redacted] of Drug Substance (See Attachment A)

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

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

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

Sincerely,

[redacted]

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

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

Danco Laboratories, LLC

May 3, 2000

ORIGINAL

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

ORIG AMENDMENT

BC

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

Dear

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

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

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

Sincerely,

/S/

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Danco Laboratories, LLC

May 11, 2000

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

ORIG AMENDMENT

BC

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

Dear

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

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

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

Sincerely,

/S/

Enclosures

cc: Sandra P. Arnold – Population Council

Nancy L. Buc, Esq. – Buc & Beardsley

Frederick H. Schmidt – Population Council

Patricia C. Vaughan, Esq. – Population Council

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

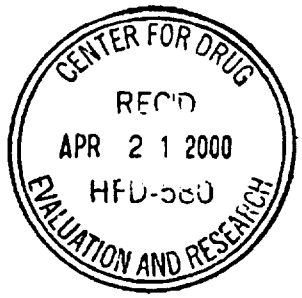
Danco Laboratories, LLC

April 20, 2000

ORIG AMENDMENT

[redacted]

13C



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

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

- Amendment 044 - Submission of Updated and Additional Stability Data

Dear [redacted]

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

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

These new data are enclosed as Attachment 1 together with copies of prior stability data on the same batches for your reference. In addition, we have updated with the new data, the graphs originally presented in our Amendment 040 comparing the stability data for our Drug Product to Roussel Drug Product. These graphs are enclosed as Attachment 2. Danco produced Drug Product continues to demonstrate good stability and the results remain comparable to the original Roussel Drug Product. These data further support our proposal for a [redacted] herein for your reference.

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

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

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

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

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

Sincerely,

/S/

[redacted]

/dns
Enclosures

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

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

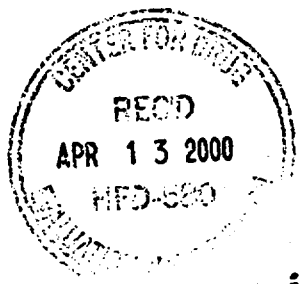
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Danco Laboratories, LLC

April 12, 2000

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



Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Disk of Labeling from Amendment #043, dated March 30, 2000

Dear

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

Please let me know if you have any questions.

Sincerely,

/S/

/dns
Enclosure

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

Nancy L. Buc – Buc & Beardsley

Population Council

noted 3/20/00 (S1)

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

Sandra P. Arnold
Vice President
Corporate Affairs

March 10, 2000

ORIGINAL

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

NEW CORRESP
NC

Att: Document Control Room 17B-20

Re: NDA 20-687

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

Very truly yours,

Sandra Arnold

cc: Nancy L. Buc, Esq.

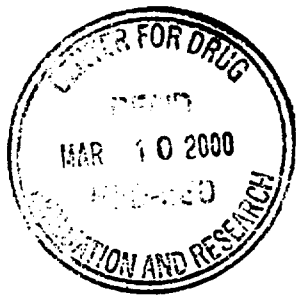
REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS /S/ DATE 3/20/00

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

Danco Laboratories, LLC

ORIGINAL

March 9, 2000



NEW CORRESP

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Request for Teleconference with

Dear [redacted]

As discussed today, given that [redacted] the Division of Reproductive and Urologic Drug Products, I would very much like to have the opportunity to have a teleconference with [redacted] is now specifically responsible for this product.

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

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

Sincerely,

/S/

[redacted]

er

/dns

cc: Sandra P. Arnold

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE 3/10/00

Danco Laboratories, LLC

[redacted]

March 6, 2000

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

ORIGINAL

NC

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

Dear [redacted]

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

Thank you.

Sincerely,

/S/

[redacted]

/dns
Enclosure

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

/S/
3/12/00

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS /S/ 6/12/00 DATE

Danco Laboratories, LLC

March 3, 2000

ORIGINAL

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

mailed 3/7/00
NC

NEW CORRES

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

Dear [redacted]

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

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

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

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

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

Sincerely,

/S/

/dns
Enclosure

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

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

APPEARS THIS WAY
ON ORIGINAL

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

FEB 2 8 2000

February 24, 2000

VIA FEDERAL EXPRESS

[redacted]

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

NEW CORRESP
N/C

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

Dea[redacted]

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

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

Very truly yours,

Sandra Arnold

Enclosure

cc: [redacted]

Frederick Schmidt, Population Council

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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

February 16, 2000

VIA FAX and FEDERAL EXPRESS

APPEARS THIS WAY
ON ORIGINAL

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

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

Dear [redacted]

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

1. **Patent Information**

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

2. **Debarment Certification**

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

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

Very truly yours,

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