emergency care in advance of prescribing the drug, including any surgical care that may be needed for treatment of incomplete abortion. Second, we suggest that the physician be urged to make sure that the patient receives the PATIENT INFORMATION and PATIENT AGREEMENT and has an opportunity to discuss them and have her questions answered.

2 and 8. Physician Training

With respect to training in the use of mifepristone for medical abortion, we have, as you suggested, revised the prescribing information and the Prescriber's Letter to state the physician's obligation to read and understand the prescribing information and to advise that his or her signature on the Prescriber's Letter constitutes an acknowledgement that she or he has done so. Specifically, we have adjusted the third bullet in the third paragraph of the Prescriber's Letter so that it now reads as follows (Refer to Attachment A: Exhibit E of the Distribution Plan, Prescriber's Letter / Order Form):

- Has read and understood the prescribing information on "Tradename." The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option, or logging on to our website, www.earlyoptionpill.com.

We have also added to the DOSAGE AND ADMINISTRATION section of the labeling (Refer to Attachment B: Marked and Unmarked Labeling) a new second sentence reading "'Tradename' should be prescribed only by physicians who have read and understood the prescribing information." We will also revise our distribution procedures to make sure that physicians who request the Prescriber's Letter receive the package insert in the materials they are sent.

3, 22, 23, and 31. Home Use versus Day 3 Visit

We continue to believe that there is no reason to require a Day 3 visit at which the patient receives misoprostol, and there are many reasons not to require such a return visit. Unlike a surgical abortion, medical abortion with mifepristone provides a woman with a greater degree of control of the process, greater involvement with the process, and, accordingly, a high degree of satisfaction precisely because so many of the choices are her own. Allowing her to choose to take her dose of misoprostol at home, in familiar surroundings, accompanied by her partner,

friends, and/or relatives, as she chooses, can only enhance her sense of autonomy.

Certainly there is no safety reason for the woman to be in the clinic rather than at home. As we discussed in our previous letter and as you implicitly acknowledged at our meeting, there is no greater safety risk in the 3-4 hours following the misoprostol dose than at any other time in the mifepristone regimen, and therefore no particular reason for a woman to be at a clinic or doctor's office during that time.

That leaves just one question: will women take their misoprostol dose if they can do so at home rather than returning to the clinic? We believe the answer is yes. The choice of medical abortion is a decision that is not reached lightly and carries with it a high level of commitment to achieving the chosen goal. That commitment will, we think, impel them to take their misoprostol. Mifepristone is different from other drugs in this respect. With most drugs, there is much less information provided to the patient before the drug is prescribed, much less patient initiative in seeking out the therapy, and much less patient involvement in deciding whether to take the drug at all. When all the patient has to go on is "my doctor told me to take it," it should be no surprise that sometimes the patient doesn't. With mifepristone, the initiative will invariably be the woman's, not the prescriber's, and that augurs well for her willingness, indeed her determination, to take the drugs as she has decided to do.

That women can and do successfully take misoprostol at home is confirmed in clinical studies, three of which are attached to this letter (Refer to Attachment C: Articles Regarding Home Use). In these studies, women self-administered misoprostol either vaginally or orally, without incident.

[redacted]

Allowing the physician and patient to choose home use of misoprostol is also very important in affording access to the mifepristone regimen. As we discussed at our meeting, requiring a Day 3 visit has the practical effect of limiting mifepristone prescribing to Monday,

Tuesday, and Wednesday, because most doctor's offices and other clinics are not open for Day 3 visits on Saturday and Sunday. That is a 40% reduction in access days, too large a reduction to be imposed unnecessarily. Especially in light of the fact that earlier treatment is clearly desirable for this regimen, cutting out 40% of the access days is also likely to result in undesirable delay.

In terms of the patient's overall medical care, we have agreed with you that the return visit at approximately day 14 is important, and we have stressed the need for this visit throughout the labeling. The Prescriber's Letter describes this visit as "very important," the package insert raises the issue under WARNINGS, INFORMATION FOR PATIENTS, and DOSAGE AND ADMINISTRATION, the PATIENT INFORMATION addresses the need for this visit three times, and the PATIENT AGREEMENT specifically mentions it twice. With so much emphasis on the importance of the visit at about two weeks, we see no need to require a Day 3 visit as a means of encouraging a later visit. Nor do we think that requiring a Day 3 visit is likely to help persuade people to return again a third time. If anything, it is probably more likely that the patient will go for a return visit at about 14 days if she doesn't have the hassle of a Day 3 visit.

, we have also revised the labeling to focus on that point in the process. First, under DOSAGE AND ADMINISTRATION, Day Three: Misoprostol Administration, we have added to the end of the second paragraph the following sentence: "The patient should be given a phone number to call if she has questions following the administration of misoprostol." Similarly, we have revised the second bullet under How Should I Use Tradename in the PATIENT INFORMATION to add a new second sentence: "If you decide to take misoprostol at home, you will be given a phone number to call if you have questions, concerns, or problems." A similar sentence ("You will be given a telephone number which you should call if you have any questions, concerns, or problems") is already included in the What Are the Possible Side Effects of Using "Tradename" section of the PATIENT INFORMATION and in the 6th bullet of Information for Patients in the prescribing information.

10. Incidence of Need for Curettage

In our November 29, 1999 letter to [redacted] we provided the following information on this issue:

Ten (10) of the thirteen patients, in group 1, who had a medical intervention were for bleeding reasons, one (1) for bleeding/endometritis, one (1) for psychotic/depression and one (1) for anemia and difficult physical examination because of fibroids.

Thus, 11 of 827 women (1.3%) had a medical intervention for bleeding, and therefore 1% is correct.

13. Timing of Dose of Misoprostol

Although there is no evidence on this point, we have revised the labeling in this regard.

16 and 33. Contraception

As agreed at the meeting, we have revised the last sentence in the penultimate paragraph under Information for Patients so that it reads "Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse."

17. Carcinogenesis, Mutagenesis, Impairment of Fertility

As agreed at the meeting, we have made the changes suggested in [redacted] June 30 letter, except for the substitution of "delayed" for "premature" suggested at the top of page 2 of her letter. On that point, our review of the literature (Refer to Attachment D: Articles Regarding Onset of Puberty) shows that puberty was delayed in male rats but premature in female rats after exposure to mifepristone. "Premature" is therefore the correct word for female rats.

We have received [redacted]s July 25 letter and are reviewing the proposals related to the CYP450 system. We will make every effort to respond in writing as far as possible in advance of our August 4 meeting, but were unable to complete our review in time to include its results in this letter.

26. Provider Qualifications

At our meeting, you asked about revising the Prescriber Letter to add as one of the

provider qualifications the ability to perform vacuum aspiration and D&C. We continue to believe that change is not only unnecessary, but also in fact potentially counterproductive for patients.

To briefly recapitulate our key arguments, emergency care and specialized care are routinely provided in the American health care system by providers who are not necessarily the patient's "regular" physician nor the prescriber of the drug whose sequelae require the care. Whether the emergency care is for perforation of the intestines following colonoscopy, cardiovascular events, whether drug-related or not, or surgical care after a spontaneous abortion (miscarriage) in a routine uncomplicated pregnancy, the patient often goes to or is referred to emergency care providers or facilities. Having specialized emergency care available is a good thing, not a bad thing. It allows gastroenterologists, for example, to utilize their expertise in GI disease and colonoscopy without having to do surgery for which they are not trained. More important, using specialty care, including surgical and emergency care, when it is appropriate avoids putting the patient suffering the emergency in the hands of those not equipped to deal with it.

There is nothing about the care which will be attendant on prescribing of mifepristone which is any different. To the contrary, as we discussed, the emergency/surgical care for incomplete abortion and heavy bleeding following mifepristone is literally identical to the emergency/surgical care for miscarriage, i.e., spontaneous abortion. Because miscarriages occur in some 15-20% of pregnancies, the treatment protocols for the necessary emergency and surgical care that some of those women will need are well established. Obstetrician/gynecologists, family practitioners, and others who do surgery will treat such patients themselves, and practioners who do not do surgery will refer them. That is exactly what we expect to happen with mifepristone, and that will provide the patients with medical expertise when they need it at the time of prescribing as well as surgical expertise when they need it in the event of an emergency.

In our July 24 telephone call, [redacted] requested that we address your question of what percentage of family practioners and general practitioners include obstetrics and gynecology, including treatment of miscarriages, in their practices. We have been unable to locate any

information on this point, but we want to reiterate that whatever the answer, surgical care for incomplete abortion in the event of miscarriages is now handled by a combination of providers, including the physician caring for the pregnant woman, other physicians to whom she is referred for surgical and other specialized care, and emergency rooms; the same combination of providers will provide surgical care for incomplete abortion following administration of mifepristone.

[redacted] also asked that we address your question of what will happen to women who remain pregnant following administration of mifepristone. As you know, the package insert recommends that women be urged to have a surgical abortion, and we expect that providers will assist women in making the necessary arrangements.

Recognizing that mifepristone will be prescribed by practitioners with and without surgical training, however, we have revised the third bullet of the Prescriber's Letter (Attachment A) so as to focus the prescriber on the need either to be able to provide surgical care or to arrange for it. It now reads as follows:

- Ability to provide surgical intervention in cases of incomplete abortion, or have made plans to provide such care through others, and to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

We also propose the following language for inclusion in a black box warning:

> If "Tradename" results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of "Tradename."

34. PATIENT AGREEMENT

We have added a new 5th bullet reading, "I believe I am no more than 49 days pregnant." Also, we agree with you that the PATIENT AGREEMENT is not as clear as the PATIENT INFORMATION on the sequence of events, so we have added bullets to clarify the woman's understanding of the protocol, as follows:

- I understand that I will take "Tradename" in my health care provider's office.
- I understand that I will take misoprostol either at home or in the clinic 48 hours (two days) after I take Tradename."

letter requested changes in the bullet concerning the treatment procedure's not working completely, and we have made those changes.

At our July 19 meeting, you also mentioned the possibility of putting earlier in the sequence the bullet on the woman's having decided to terminate her pregnancy. We think it is more logical and more appropriate to leave it at the end, so that it follows the woman's recapitulation of the information she has received that underlies her decision to proceed and immediately precedes her signature.

Encouraging and Documenting Provision of Information to Patients

As we discussed at the meeting, we definitely agree with you that it is important for women considering medical abortion with mifepristone to receive the PATIENT INFORMATION, to read it and discuss it with their provider if they wish to, and to receive and have an opportunity to read carefully and discuss the PATIENT AGREEMENT. We also think this is not really something to worry about, because the mifepristone system is set up to encourage it and because physicians and their colleagues are these days set up to follow such information regimens.

To begin with, the labeling is already replete with references to and emphasis on the importance of the physician's providing information, both written and oral. The Prescriber's Letter, which will be the first contact for prescribers, tells the prescriber that he or she must "provide 'Tradename' in a manner consistent with the following guidelines," and puts first the need to "fully explain the procedure to each patient and obtain her signature on the PATIENT AGREEMENT". We have revised this bullet to make it clearer:

- You must fully explain the procedure to each patient, provide her with a copy of the [redacted] and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.

In addition, the Order Form for mifepristone allows both first-time and experienced prescribers to order more copies of the PATIENT INFORMATION and the PATIENT AGREEMENT, and the distributors will offer everyone who re-orders the drug additional copies. These documents will also be printable off Danco's website. There are also frequent references in the package

insert (under Contraindications, Information for Patients, and Dosage and Administration) to the need for the patient to receive these materials and to be given copies.

With so much prompting, physicians and their colleagues are likely, we think, to incorporate the provision of written and oral information in their office protocols as a matter of routine. To provide still further reminders, Danco has decided to have its distributors send each prescriber quarterly for the first year and annually thereafter a reminder of the importance of providing the PATIENT INFORMATION and PATIENT AGREEMENT to patients. In addition, we will include in a black box warning the following:

> Prescribers should make sure that patients receive and have an opportunity to discuss the [redacted] and the PATIENT AGREEMENT.

* * *

We look forward to meeting with you and your colleagues on August 4, and to working together to resolve the remaining issues.

Very truly yours,

Sandra Arnold

APPEARS THIS WAY
ON ORIGINAL

Population Council

BUC & BEARDSLEY
919 Eighteenth Street, N.W.
Suite 600
Washington, D.C. 20006-5503
(202) 736-3600
(202) 736-3608 (fax)

Sandra P. Arnold
Vice President
Corporate Affairs

FACSIMILE TRANSMISSION

September 26, 2000

Please deliver to: [redacted] (t)

From: Nancy L. Buc (202) 736-3608 (f) (202) 736-3610 (t)
Sender's Direct Dial

Total Pages (including cover sheet): 4

COMMENT:

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If you do not receive legible copies of all pages, please call (202) 736-3600.

The Population Council

Center for
Biomedical Research

ORIGINAL

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Telex: 238274 POBI UR

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

/S/ 6/7/95

CSO INITIALS DATE

noted
10/31/94
/S/
PC, PI

27 October 1994

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

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D OCT 28 1994 HFD-510

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number:
Protocol Amendment- Change in Protocol
New Investigators

/S/
6 Jun 95

Dear ———:

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment

A. Change in Protocol and Informed Consent Document

Attachment 1 contains a revised version (dated October 13, 1994) of Protocol 166 A - "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days" and the recommended Informed Consent Document. The original versions of this protocol and the consent document were included in Submission 100 (August 3, 1994). Revisions were also made to the documents as described in Submission 104 (October 6, 1994).

Appended to the revised documents is a listing of the changes made from the earlier versions.

Please note that the Informed Consent Document is the consent document recommended by The Population Council for use by investigators. Some individual study sites may make modifications to the document. In addition,

please also note in Part 2 (Summary of Study) of the protocol that patients will be enrolled in this protocol and an identical sister protocol, to be conducted simultaneously. The latter protocol is not being submitted because it is identical to Protocol 166 A. However, for distinction in study records, the sister protocol has been designated as Protocol 166 B.

B. New Investigators

Attachment 2 contains Statement of Investigator forms (Form FDA 1572) and curricula vitae for the following three new investigators who will conduct studies under Protocol 166A or B:

Susan C. A. Haskell, D.O.
Planned Parenthood of Greater Iowa
Des Moines, IA 50314

Katharine L. Sheehan, M.D.
Planned Parenthood
San Diego, CA 92108

Peter A. Vargas, M.D.
Planned Parenthood of the Rocky Mountains
Denver, CO 80205

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

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin, M.D.
Director

APPEARS THIS WAY
ON ORIGINAL

Attachments

Attachment 1

Revised Protocol and Informed Consent Document

APPEARS THIS WAY
ON ORIGINAL

MIFEPRISTONE STUDY
MODIFICATIONS TO THE PROTOCOL
FOLLOWING THE OCTOBER 3-4, 1994
INVESTIGATOR'S MEETING

Protocol:

Cover Sheet:	Change: The Population Council to The Population Council, Inc.
	Change: Written authorization from The Population Council, to written authorization of The Population Council
Table of Contents: 6.5:	Change: SAFETY ASSESSMENT COMMITTEE to MEDICAL ADVISORY COMMITTEE
P. 3: First paragraph:	The word either was added in reference to parenteral or prostaglandins in combination with mifepristone
P. 3: Last paragraph:	Change: heart condition to heart complications
P. 4: Third paragraph:	Change: as close as possible to as closely as possible
P. 4: Last paragraph	Add: Subject shall visit the study center three times **unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin.**
	Add: At the initial visit (Day 1) ; **after any required statutory waiting period.**
P.5: second paragraph:	Change: institutional insurance to general liability insurance
P.6:	**Add: 4.1.3 Residents of the United States**
P. 6:	**Add: 4.2.9 Resident of the United States**
P. 7: 4.3.2	delete
P. 7: 4.3.5	Add: **or hematocrit below 30%**
P. 7: 4.3.7	Delete
	Add: **Subjects with an IUD in place.**

P. 7: 4.3.15 -		Change to:	Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place of work and (b) the abortion center.
P. 8: Section 5.2:		Clarification that 600 mg of mifepristone will be administered orally.	
P. 9: Section 5.3:	A)	Change to:	Mifepristone will be provided as 200 mg tablets of micronized mifepristone
	B)	Change to:	Misoprostol will be obtained locally by each investigator as 200 µg tablets of commercially available misoprostol.
P. 9: Section 5.4:	A)	Change to:	Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.
	B)	Change to:	Misoprostol will be obtained locally by each nvestigator as 200 µg tablets of commercially available misoprostol and dispensed from the center pharmacy.
P. 9: Section 5.5: paragraph 1		Change:	——— hypotension
		Change:	should be avoided to **must** be avoided
P. 10: Section 6.1:		Change:	Serum ßhCG test to quantitative serum ßhCG.
		Change:	Determination ——— and Rh status to Determination of Rh status and where routinely collected, the blood group.
P. 10: - Last paragraph:		Add:	**No more than** 240 ml.

P. 11:	Second paragraph:	Change:	Subjects will be given written information to Subjects will be given a copy of the informed consent and patient diary card.
		Change:	..... which receives patients ..... **to which cares** for patients
	Section 6.2:	Add:	**If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.**
	Last paragraph:	Delete:	~~———~~
		Add:	**, if indicated.**
P. 12:	First paragraph :	Add:	**No more than** 240 ml
	Second paragraph: Last sentence	Delete:	~~———~~
P. 13:	Section 6.2: Second to Last paragraph	9/6/94 last paragraph Changed to:	A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.
P. 13:	Section 6.2: Last paragraph	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**

P. 13: Section 6.3:	Add:	**Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.**
P. 14: after last paragraph	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 15: Section 6.5:	Change Heading:	Safety Assessment Committee to Medical Advisory Committee.
	Change Body:	Safety Assessment Committee to Medical Advisory Committee
P. 16: Section 6.7: first paragraph	Add:	**A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**
P. 16: Section 6.7: Second paragraph	Change:	~~___~~ to 60 hours
P. 18: Section A:	Change:	study drug to study drugs.
P. 20: Section D:	Add:	**Except as otherwise explicitly set forth herein,**
P. 21: Seventh paragraph:	Change:	submitted for histological examination to submitted for pathological examination
P. 27:	Add:	**Hemoglobin or Hematocrit Determination, Quant. Serum ßhCG**
	Change:	Administration ~~_____~~ Administration of anti-D globulin

Informed Consent:

Section 1 Change: _____ to over 150,000

Section 2 Clinic Visits:
Second paragraph last sentence:

Change: or third visit to, visit 3,

Section 2 Clinic Visits: Add: paragraph 4

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

Section 8: After last paragraph
Add: **I understand that, if my treatment under the study does not result in an abortion, and I refuse surgical abortion and continue my pregnancy, I risk, and the infant may risk, complications including fetal or infant malformation.**

APPEARS THIS WAY
ON ORIGINAL

ne Population Council
nter for
omedical Research

ORIGINAL

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

[redacted]

3/15/95
/S/

March 6, 1995

S2

BY FedEx

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 09 1995
HFD-510

Subject: **IND No. [redacted]-Mifepristone Tablets, 200mg**
Submission Serial Number: 121
IND Safety Report

/S/
15 Mar 95

Dear [redacted]

Please find enclosed FDA Form 3500 for an adverse event reported to the Population Council in the above referenced study.

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

CWB:fia

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☑ N.A.

/S/ 3/17/95

The Population Council
Center for
nedical Research

ORIGINAL

N-120
52

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Printed
3/8/95
/S/

March 3, 1995

BY FedEx

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

Subject: **IND No. ——— Mifepristone Tablets, 200mg**
Submission Serial Number: 120
IND Safety Report

Printed
/S/
15 Mar 95

Dear ———

Please find enclosed a copy of FDA Form 3500 for to an adverse event reported to you in a telephone report on February 24, 1995 by Fred Schmidt of the Population Council in the above referenced study. The event occurred ——— whereas it is not directly stated on the form. ———

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

/S/ 3/15/95

C. Wayne Bardin

CWB:sh

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG
REC'D
MAR 06 1995
HFD-510
EVALUATION AND RESEARCH

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ORIGINAL
N 119 (S2)

/S/ 2/27/95

February 17, 1995

BY Fed Ex

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

/S/ 2/27/95

Subject: **IND No. ——Mifepristone Tablets, 200mg**
Submission Serial Number: 119
IND Safety Report

Dear ——

Please find enclosed copies of FDA Forms 3500 in reference to adverse events reported to you in a telephone report on February 10, 1995 —— page 01) and February 17, 1995 —— pages 02 and 03) by Fred Schmidt of the Population Council in the above referenced study.

If you require any additional information, please contact me.

Sincerely yours,

C.W Bardin

C. Wayne Bardin

CWB:fia

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.

/S/ 2/27/95

CSO DATE

ORIGINAL
S2

The Population Council
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[redacted]

mailed
2/22/95
/S/

February 15, 1995

/S/
22 Feb 95

BY Fed Ex

[redacted]

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

Subject: **IND No. [redacted] Mifepristone Tablets, 200mg**
Submission Serial Number: 118
IND Safety Reports

Dear [redacted]

Please find enclosed copies of FDA Form 3500 in reference to five adverse events reported to The Population Council in the above referenced study.

If you require any additional information please contact me.

Sincerely yours,

C W Bardin

C. Wayne Bardin

CWB:sw

FOR BLUE
RECD
FEB 17 1995
HFD-510
EVALUATION

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER /S/ ☒ N.A.I. 2/22/95
SIGNATURES DATE

The Population Council
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Telephone: (212) 327-8731
Telex: 238274 POBI UR

[redacted]

Mailed 2/15/95 /S/

February 9, 1995

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

ORIGINAL

Mailed /S/ 15 FEB 95

Subject: **IND No. [redacted] Mifepristone Tablets, 200mg**
Submission Serial Number: 117
Information Amendment: Clinical (Audit of Pivotal French Studies)

Dear [redacted]

In reference to our submission of January 4, 1995, Serial Number 112, Appendix 3, enclosed is a medical evaluation of the audit report prepared by [redacted] dated December 9, 1994 on the coding of text files used by Roussel Uclaf for their two French Studies 9114 and 9224. [redacted] reviewed [redacted] report and found the low rate and types of discrepancies observed by [redacted] in their audit of studies 9114 and 9224 would not affect conclusions regarding either safety or efficacy of these two pivotal French Studies. A copy of [redacted] evaluation is attached.

If you require any additional information please contact me.

Sincerely yours,

[redacted] Wayne Bardin

CWB:sw [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D FEB 10 1995 HFD-510

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER /S/ 2/17/95 ☒ N.A.I.

CSO INITIALS / / DATE

[redacted]

[redacted]

5 January 1995

Dear [redacted]

Based on our review of the memorandum "Coding of Text Fields in French Studies 9114 and 9224" dated December 9, 1994 we have arrived at the following conclusions regarding the databases for studies 9114 and 9224:

1. The low rate of discrepancies between the case report forms and databases in text coded fields and the low rate of inconsistencies among text coded fields will not affect conclusions regarding either the safety or efficacy of the procedures used the studies.

2. The types of discrepancies/inconsistencies found will not affect conclusions regarding either the safety or efficacy of the procedures used in the studies.

3. The low rate and types of discrepancies found in the 20% audits does not necessitate an audit of the unauditied case report forms and/or text coded fields.

4. Incorrect information in the databases found in the audits, that affects the analyses of the data, should be corrected. For example, missing adverse event codes should be added to the database, but there is no need to correct text field information on ultrasound examinations if the information in these fields does not affect the estimate of gestational age.

Sincerely,

[redacted]

1

[redacted]

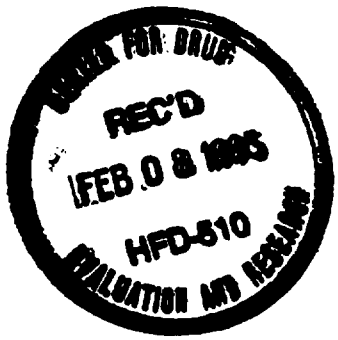
e Population Council

ter for
medical Research

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

ORIGINAL

2/14/95
/S/



February 7, 1995

BY FEDEX

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

Subject: IND —— Mifepristone Tablets, 200mg
Submission Serial Number: 115
IND Safety Report

2/14/95
/S/

Dear ——

Please find enclosed a copy of FDA Form 3500 in reference to an adverse event reported to the Population Council in the above referenced study.

If you require any additional information, please contact me.

Sincerely yours,

/S/ for

C. Wayne Bardin

CWB:fia

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☑ NAI

/S/ 2/14/95

CSO INITIALS

MIF 004724

e Population Council
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2/1/95
/S/

1230 York Avenue
New York, New York 10021
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January 23, 1995

SB

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

/S/ 2/1/95

Subject: IND — Mifepristone Tablets, 200mg
Submission Serial Number: 114
IND Safety Report

Dear —

Please find enclosed copies of FDA Forms 3500 in reference to two adverse events reported to the Population Council in the above referenced study.

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

CWB:fia

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER /S/ 2/1/95 ☐ N.A.I.

CSO INITIALS

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S2
ORIGINAL

January 18, 1995

Noted
1/27/95
/S/

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

Subject: IND ——— Mifepristone Tablets, 200mg
Submission Serial Number: 113
IND Safety Report

Dear ———

Please find enclosed copies of FDA Form 3500 in reference to five adverse events reported to the Population Council in the above referenced study.

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

/S/

CWB:fia

REVIEWS COMPLETED

CSO ACTION:

☐ IND ☐ N.A.I.

/S/ 1/20/97

CSO INITIALS

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EVALUATION AND

The Population Council
Center for Biomedical Research

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noted 1/18/95 /S/

January 4, 1995

ORIGINAL

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

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number : 112
Information Amendment : Clinical (Audit of Pivotal French Studies)

Dear —

As outlined at our meeting with you at the FDA on July 7, 1994, Roussel Uclaf has conducted two separate clinical studies on the use of mifepristone plus misoprostol in the termination of pregnancy. At that meeting, the Population Council proposed that these two studies be used as the pivotal studies in the clinical section of the NDA.

This letter is to appraise you of the status of our evaluation of these two studies, designated French Study 9114 and French Study 9224, or abbreviated as study 14 and study 24, respectively. A site visit was conducted between September 12-16, 1994 by — Vice President, Corporate Affairs and — Clinical Program Manager from — as well as their French subsidiary, — Members of this team were — and — In addition, — and — from — participated in this site visit.

APPEARS THIS WAY
ON ORIGINAL

The aim of the group from —— was to evaluate the availability and completeness of the regulatory documents associated with each study, on file at Roussel's headquarters. In addition, trips were made to two investigational sites, to assess the status of source documentation, case record forms and on-site regulatory documentation. The group from —— evaluated the completeness and accuracy of Roussel's transfer of information from case record forms to their electronic data base.

In —— report, (Appendix 1) they have provided a detailed overview of these two studies (study numbers 14 and 24). They have also reviewed the availability and completeness of regulatory documents which were present at the Roussel headquarters and reported on the status of clinical data at two individual clinics (Dr. Aubeny and Dr. Dreyfus).

In —— report dated November 30 (Appendix 2), they conducted an audit of Roussel's electronic database, which contained the information transfered from case record forms. —— report dated December 9 (Appendix 3) is a further description of one aspect of this audit, specifically related to the coding of text fields used by Roussel.

These three reports provide a comprehensive overview of the status of the clinical data from the two French pivotal studies 9114 and 9224 we propose to use in the NDA application. Additional activities associated with the assessment of these studies, currently underway or planned, are the following:

1. —— will audit five individual clinics where the majority of the subjects have been studied. These clinics are listed in the Table 1. At each of these sites, an in depth audit of the case record forms of 10% of the subjects will be evaluated to determine if data from subjects' records were accurately transposed onto case record forms. In addition all regulatory documents will be assessed at these sites. This process has already been conducted in the clinics of Dr. Aubeny and Dr. Vitani. The other three clinics are scheduled to be evaluated within the coming

weeks.

2. A medical evaluation of the information contained in the coded text fields described in Appendix 3 is being conducted by —

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin

Attachments
Table 1
Appendix 1: Report dated December 1, 1994 from —
Appendix 2: Report dated November 30, 1994 from —
Appendix 3: Report dated December 9, 1994 from —

APPEARS THIS WAY
ON ORIGINAL

Table 1

Investigator	*No. Subjects Enrolled*	
	Study 1	Study 2
Dr. Aubeny	210	219
Dr. Vitani	72	60
Dr. Van Geem	120	190
Dr. Neny	54	88
Dr. Jourdan	27	119
Enrollment	483	676

SUMMARY OF SITE VISIT TO ROUSSEL FOR THE MIFEPRISTONE - MISOPROSTOL COMBINATION

Between September 12 - 16, 1994, [redacted], Clinical Program Manager, and I met with representatives of the [redacted] and Roussel for the purpose of determining the availability of data from the studies conducted in France (Study numbers 14 and 24). In addition the visit was planned to determine future requirements for completing the evaluation of the data and establish on-site auditing procedures.

On September 11th, [redacted] and I went to [redacted] and had the opportunity to meet with [redacted] to discuss the overall plans for the audit. On September 12th, [redacted] and I met with the staff of [redacted] and reviewed the SOPs for auditing and monitoring. We found these SOPs to be complete and compatible with the requirements established by FDA.

We had the opportunity to review the proposed program with the two auditors from [redacted] Clinical Program Managers. The protocol had been forwarded to them in advance of our meeting along with a copy of the case report forms for the study number 14. We reviewed these documents and discussed the potential auditing program which included on-site visits for up to 15 investigational sites that had participated in the study.

In the afternoon we met with Dr. Remi Peyron, Head of the Endocrinology Division for Roussel, for domestic studies. This meeting took place at Roussel facility, rue de Vaugirard. During this initial meeting we also met with two representatives of [redacted] Thereafter the [redacted] representatives worked independently of the clinical audit team.

We discussed the audit program and schedule and Dr. Peyron summarized the studies that had been conducted by Roussel. He informed us that the study number 14 had been conducted under the overall supervision of Dr. Elizabeth Aubeny and had enrollment of 1286 patients at 25 centers. This study conducted by Roussel was initiated at the request of the French Ministry of Health because the combination of mifepristone and sulprostone, the already marketed combination, had resulted in the death of a patient in France. Study number 14 was designed for women with less than a 49 day gestational age, and the combination used was 600 mg of mifepristone and 400 μg of misoprostol. Dr. Peyron explained that in study number 14 the protocol had originally been designed for enrollment of 500 patients.

All documentation provided to the French Ministry of Health was approved for the enrollment of 1,000 patients. The protocol was amended to increase the patient population of 1000 patient enrollment and to extend enrollment until the product had marketing approval. The informed consent was unchanged and still represented a total enrollment of 500 patients.

Dr. Peyron informed us that the additional 286 patients (those patients over the 1000 that were approved) had been entered as Roussel was unable to determine the exact number of patients enrolled at the 25 locations. When the decision was made to stop the study, significantly more patients had entered than had been originally been planned.

Following the completion of the 1286 patients, an amendment was approved by the Ministry to allow the study to be extended under much less rigorous conditions. As a result, the case report forms were changed and some of the evaluations were made unnecessary. This accounts for an additional enrollment of 744 patients into study number 14. Dr. Peyron explained that the extension was still conducted under Good Clinical Practices Regulations and that informed consent forms were signed as well as monitoring visits made to the sites. The case report forms were green for the initial study and blue for the extension.

Protocol number 24 was also discussed. This study differed from study number 14 in two aspects, the gestational age of the patient was increased to 63 days, and if expulsion did not occur within 3 hours after the misoprostol dose, an additional 200 μg (one tablet) of misoprostol could be administered. This study had an actual enrollment of 1195 patients, however 1200 patient numbers were used because four (4) patients vomited the mifepristone soon after its ingestion and one patient's tablets were broken. All of these patients were assigned a new patient number.

We were informed that study number 24 was completed and all case report forms were retrieved and in-house at Roussel, rue de Vaugirard. This study was conducted from December 1992 - July 1993 with 11 investigational sites. The CRFs were accounted for at Roussel and each of the 11 investigator files were audited by the audit team. Each of the investigators that participated in study number 24 also participated in study number 14.

Dr. Peyron explained that the results of study number 24 would not be submitted to the French Ministry of Health for the additional indication of up to 63 days of gestation. Although a final analysis is ongoing, the analysis to date showed that with increased gestational age, the mifepristone/misoprostol combination was not as effective and the side effect profile was enhanced.

In review of both study files, it was noted that various documentation was missing. A listing, in French, was presented to Roussel management so that the files could be more complete.

During our five day audit, trips were made to Investigative sites, (Dr. Aubeny, Dr. Dreyfus) to assess the status of the source documentation and case report forms, and to inform the investigators of the upcoming potential auditing program. Introductions were made identifying ——— as the team who would be responsible for performing these audits. Both centers had medical records available which provided verification to entries on the CRF. The degree of documentation was not assessed at this time. A brief audit of all on-site regulatory documentation noted compliance with regard to informed consents.

Once centers are identified for audit, Dr. Peyron, Roussel should be informed so that he can alert the centers to these visits. Dr. Peyron stated that a 30 day notice should be given so centers can prepare appropriately.

We were also informed that two additional studies were conducted independently of

Roussel. The investigators who conducted these additional studies were Dr. Aubeny and Professor Baulieu. The first study was a 100 patient pilot study. The mifepristone/misoprostol combination, 600 mg and 400 μg respectively, was administered to women with up to 49 days of gestation. The results of this study initiated the start-up of study number 14.

The second study enrolled 390 patients. The study was similar to the pilot study with two exceptions. A second dose of misoprostol (200 μg) was administered if expulsion did not occur within 3 hours of the first dose of misoprostol (400 μg). Also, the gestational age was increased to 63 days or less.

Both studies were analyzed and published. The publication reference for the 100 patient pilot study is to be provided by Roussel for our records and the results of the second study were published in the New England Journal of Medicine, May 1993.

Attached is a listing of all investigational sites that participated in study number 14 and 24 and a detailed list of the findings from this audit.

Vice President - Corporate Affairs

Program Manager

The Population Council
Center for
medical Research

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New York, New York 10021
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12/28/94
/S/

BEST POSSIBLE COPY

December 20, 1994

BY FEDEX

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

/S/

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial #110
IND Safety Report

Dear ——

Please find enclosed a copy of FDA Form 3500 in reference to the adverse event reported to you on December 14, 1994 by Fred Schmidt of the Population Council in the above referenced study.

If you require any additional information please contact me.

Sincerely,

C. Wayne Bardin, M.D.

REVIEWS COMPLETED
CSO ACTION:
☐ IF ☒ N.A.I.
/S/ 1/3/97
CSO INITIALS DATE

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DEC 2/3/1994
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ORIGINAL

/S/

December 22, 1994

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

Subject: **IND — , Mifepristone Tablets, 200mg**
Submission Serial Number: 111
Protocol Amendment - New Investigator,
Pilot Study Status Report

Dear —

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend the application to provide for a new investigator and to inform you of the status of the pilot study segment of our clinical program.

1. New Investigator

Attached is a Statement of Investigator form (Form FDA 1572) and curriculum vitae for the following new investigator who will conduct studies under Protocol 166B, as submitted October 27, 1994 -- Submission Serial Number 105:

— — Mark D. Nichols, M.D.
Downtown Women's Center
Portland, OR 97201

2. Pilot Study Status Report

In Submission Number 100, dated August 3, 1994, we had proposed that a pilot study be conducted at three or four clinics. The objective of the pilot study, to be conducted under Protocol 166A, as included in that submission, was to assess the feasibility of the protocol and the adequacy of the case record forms. It was anticipated that the study would be completed by September 15 and would include 15 patients at each clinic for a total of 45 to 60 patients.

We were able to initiate the pilot study at only one clinic, that of Dr. Daniel Mishell, Jr., in Los Angeles, CA. At that clinic, the study was extended through November 16, 1994

and a total of 42 patients was enrolled. Based on the general experience with these patients, we judged that the clinical protocol and case report forms were appropriate for the larger clinical program in this country.

Dr. Mishell has now switched to the amended clinical protocol which was forwarded in Submission 105 and continues his study which includes several additional procedures as outlined in Submission 106, dated November 21, 1994.

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

Sincerely,

C. Wayne Bardin

C. Wayne Bardin

Attachments

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ON ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ E.L.
/S/ 1/10/95
CSO INITIALS

The Population Council
Center for
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1230 York Avenue
New York, New York 10021
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December 7, 1994

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12/14/94
/S/

BY FEDEX

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

Subject: IND [redacted] Mifepristone Tablets, 200mg
Submission Serial Number: 109
IND Safety Report

Dear [redacted]

Enclosed please find information on three (3) adverse events for the above referenced study. These include: (1) an adverse event reported to [redacted] of the Agency on December 1, 1994 by Dr. Irving Spitz of the Population Council [redacted], pp. 01-02); [redacted], pp. 03-04); and (3) a typed version of FDA 3500 Form identical to the handwritten report submitted as Serial Number 107 on November 21, 1994 (p. 05). Included in the report for adverse events (1) and (2) above is a copy of the text prepared by the physician at the site where the event occurred.

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

If you ~~have~~ require any additional information please contact me.

Sincerely,

CW Bardin

C. Wayne Bardin

CWB:sh

CENTER FOR DRUG REC'D DEC 09 1994

REVIEWS COMPLETED

CSO [redacted]:

☐ [redacted] ☐ N.A.I.

/S/ 12/16/94

CSO INITIALS / DATE

MIF 004738

The Population Council
Center for
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Mailed 12/7/94

ORIGINAL /S/

December 1, 1994

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BY FEDEX

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

Subject: IND —— Mifepristone Tablets, 200mg
Submission Serial Number: 108
IND Safety Report

Dear ——

Please find enclosed copies of FDA Form 3500 for two incidents which occurred at one of the study sites in the above referenced study. Neither incident was life threatening nor required hospitalization. However we felt your office should be informed.

If you require any additional information please contact me.

Sincerely,

/S/

for C. Wayne Bardin

CWB:sw

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EVALUATION AND RESEARCH

REVIEWS COMPLETED

CSO ACTION:
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/S/ 12/05/94
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ORIGINAL

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Noted
12/1/94
/S/

November 21, 1994

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

Subject: IND [redacted] · Mifepristone Tablets, 200 mg
Submission Serial #107
IND Safety Report

Noted
/S/
12-2-94

Dear [redacted]

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

If you require any additional information please contact me.

Sincerely,

C.W. Bardin

C. Wayne Bardin, M.D.
Director

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I.

/S/ 12/1/94
CSO INITIALS DATE

The Population Council
Center for
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ORIGINAL

November 21, 1994

Noted
11/28/94

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

Subject: IND —— **Mifepristone Tablets, 200 mg**
Submission Serial Number: 106
Protocol Amendment- New Investigators

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment

A. **New Investigators**

Attachment One contains Statement of Investigator forms (Form FDA 1572) and curricula vitae for the following four new investigators who will conduct studies under Protocol 166A or B, as submitted October 27, 1994 -- Submission Serial Number 105:

——

Suzanne T. Poppema, M.D.
Aurora Medical Services, Inc.
Seattle, WA 98133

[ ]

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I.
/S/ 12/12/94
CSO INITIALS DATE

RECD NOV 23 1994 HFD-510 RESEARCH

MIF 004741

A. New Investigators (Cont.)

J. Tyson, M.D.
Planned Parenthood of Northern New England
Williston, VT 05495

Carolyn L. Westhoff, M.D.
Columbia Presbyterian Medical Center
New York, NY 10032

B. Revised Documentation -- Current Investigator

Attachment Two contains a revised Statement of Investigator form for

Daniel R. Mishell, M.D.
University of Southern California Medical Center
Los Angeles, CA 90033.

for whom original investigator documentation was submitted on October 6, 1994 -- Submission Serial Number 104. The original Statement of Investigator form has been revised to correct a misspelling in the name of the investigator and to provide for a change in subinvestigators in the study.

Further, we wish to advise you that in addition to the procedures outlined in the study protocol, Dr. Mishell conducts the following procedures in his study:

Visit 1	STD Screening Pap Smear CBC
Visit 2	Ultrasound, which is optional in the protocol, is always performed and an additional second ultrasound procedure is performed four hours after misoprostol administration
Visit 3	Ultrasound and βhCG, which are optional in the protocol, are always performed

B. Revised Documentation -- Current Investigator (Cont.)

These additional procedures, which have been approved by the local Institutional Review Board, are not considered to affect the quality of the data collected in the study.

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

Sincerely yours,

C. Wayne Bardin, M.D.
Director

Attachments

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
medical Research

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June 5, 1995

noted
6/6/95
/S/

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

dated
/S/
8/23/95

/S/

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 131
General Correspondence

Dear ——

As you are aware, we are presently compiling the information available to us on mifepristone into a New Drug Application for submission later this year. At this time we would like to present you with an preview of how we anticipate the application to be assembled and to present several issues regarding the clinical portion of the submission on which we would appreciate your comment.

The NDA will be comprised primarily of chemistry, manufacturing and controls, preclinical pharmacology and toxicology, and clinical information which has been provided to us by Roussel Uclaf, the product manufacturer. This information was also provided directly to your agency by Roussel in 1993. The application will include a "right of reference or use" authorization from Roussel to the total body of information available.

We currently anticipate that the major components of the application will be developed as follows:

Item 2: Summary

The summary of the application will be prepared in accordance with the Guideline for the Format and Content of the Summary for New Drug and Antibiotic Applications" (2/87).

Item 3: Chemistry, Manufacturing and Controls

This section will be prepared as outlined in the "Guideline for the Format and Content of the Chemistry, Manufacturing and Controls Section of an Application" (2/87) and related guidelines for preparation of this portion of the application. The content of the section will be assembled based on information provided by Roussel Uclaf to

permit that company to supply the drug product in this country.

Alternative suppliers of the new drug substance and of the new drug product have been identified and the firms are now developing production capabilities. Information on these parties will be submitted to the NDA as an amendment or supplement in the future.

Item 5: Nonclinical Pharmacology and Toxicology Section

All information to be submitted in this section has been previously submitted under IND —— The order of presentation of the information will be as described in the "Guideline for the Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application" (2/87). Included in the section will be an expanded table of contents for the section, summary narrative and tabular information on the contents, and full reports of nonclinical studies.

Item 6: Human Pharmacokinetics and Bioavailability Section

All information to be submitted in this section has also been previously submitted under IND —— This section will be organized and information presented as recommended in the "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application" (2/87).

Items 8 and 10: Clinical Data and Statistical Sections

These sections will be organized along the general format as recommended in the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application" (2/87); however, due to the nature of the drug and the available information, there will be some deviations as discussed below:

Overview of Available Clinical Information

Clinical information included in the application will consist of pharmacology and efficacy and safety studies which have been performed in other countries over the last 12 years. Apparently because of the time span over which the foreign studies were conducted, not all studies contain specific information on items such as the qualifications of investigators, description of facilities, and details of compliance with ethical principles as required by current regulations and current concepts of good clinical practices. To address this matter, we propose to ask Roussel to provide a general confirmation that all studies were performed by qualified investigators in appropriate facilities and in accordance with the principles of the Declaration of Helsinki and the ethical standards of the respective countries where the studies were conducted. Please advise us if this approach will be acceptable to the FDA.

As outlined below, two French studies have been designated as pivotal in the demonstration of efficacy and safety of the product. The studies have been audited and re-analyzed by The Population Council and tabulations of patient data for the two studies will be included in the submission. These studies each involve a single treatment group and are considered as historically-controlled. It is our understanding from our meetings with your division on July 16, 1993 and July 7, 1994 that the design of the studies will be acceptable for the demonstration of efficacy and safety.

Currently we are conducting two clinical trials with mifepristone and misoprostol as an abortifacient in women with amenorrhea of ≤ 63 days. As an interim report, a list of the adverse events that have occurred during the trials will be included in our initial application. When the trials are complete, the results will be submitted as an amendment to the application.

In accordance with the FDA guidelines, clinical information will be presented in major groupings as follows:

1. Clinical Pharmacology

The section will include studies to characterize the pharmacokinetic/bioavailability and pharmacologic characteristics of the product alone and with prostaglandin. Studies will be presented in the format recommended in the guidelines.

2. Controlled Clinical Trials (Historical Controls)

Pivotal Studies: Mifepristone plus Misoprostol - Phase 3

Study 1 - Mifepristone (600mg) and misoprostol (400 μg) in women with amenorrhea of ≤ 49 days (1,205 patients evaluable for efficacy and 1,286 patients evaluable for safety).

Study 2 - Mifepristone (600 mg) and misoprostol (400 or 600 μg) in women with amenorrhea of ≤ 63 days (1,105 patients evaluable for efficacy and 1,194 evaluable for safety). The results of this study were not written into an official study report by Roussel Uclaf. A summary, however, was sent to the Population Council by Dr. Ulmann in the summer of 1994 indicating that women were offered a second dose of 200 μg of misoprostol if the first dose of this drug (400 μg) did not produce an abortion within four hours while the women were in the clinic. The Council was informed that 210 women with amenorrhea of equal to or less than 49 days elected not to take a second dose of misoprostol. This information was presented to the FDA by Council staff during the meeting with the FDA on 7 July 1994. At this meeting, it was agreed that the data from these 210 women mentioned above could be used as a second pivotal study in the Council's NDA application. The Council has now translated the protocol for this study and analyzed the results. Contrary to what we were told by Roussel staff, the protocol states that **all** women who did not abort while in the clinic should receive the second dose of misoprostol and this was indeed how the trial was conducted. The 210 women that did not get the second dose were made up primarily of those who aborted while in the clinic. In view of the fact that the study was conducted by a protocol that was different from that represented to the

FDA on 7 July 1994, the Council will not only present an analysis of the 210 patients that received a single dose of misoprostol but will also present an analysis of all the other groups of women who participated in this study. In the opinion of Council staff, this is the most informative and least biased way to present these results. Therefore, the results from subsets of patients receiving one or two doses of misoprostol and those with ≤ 49 days of amenorrhea or 50 to ≤ 63 days of amenorrhea will be analyzed.

Other Historically-Controlled Clinical Trials

- Efficacy and tolerance studies using mifepristone alone - Phase 2 (n = 9)

- Efficacy and tolerance studies using mifepristone alone - Phase 3 (n = 9)

- Efficacy and tolerance studies using mifepristone (600 mg) in combination with a prostaglandin - Phase 3 (n = 9)

3. *Uncontrolled Clinical Trials*

All studies conducted with mifepristone in the induction of abortion can be regarded as having historical controls which consist of the body of information available on abortion using surgical procedures.

4. *Other Studies and Information*

- Studies in other indications

[ ]

- Commercial marketing experience

- Literature reports

*** ***

Reports of the studies and documents mentioned in the above groupings will be presented in the format outlined in the guidelines. Reports of clinical studies will include a brief synopsis (see example in Attachment 1) along with a more comprehensive summary (see example in Attachment 2) followed by the full clinical/statistical report and other information (protocol, publications, etc.)

5. *Integrated Summary of Efficacy*

This section will follow closely the recommended format in the clinical guidelines; however, it will focus primarily on the two designated pivotal studies, which are the

only two that used the combination of mifepristone and misoprostol.

6. Integrated Summary of Safety

This section will also follow closely the recommended format in the guidelines.

Overall safety data from all clinical studies, for abortifacient as well as other indications, will be presented in this section. Due to the different protocol requirements, drug regimens and doses used in the studies, the type, frequency and severity of adverse events reported will be summarized separately for several groups:

- Abortifacient use:

  -- mifepristone alone
  -- mifepristone plus other prostaglandins
  -- mifepristone plus misoprostol (the two pivotal studies)

- Other indications:

  -- mifepristone alone

The section will also include a summary report on the clinical laboratory data available in all other studies in the submission. An overall statistical analysis was not performed in this report; however, the document includes summary findings in each individual study and provides overall conclusions on the total database. Data listings (seven volumes) of results from each study have been prepared and, according to the preference of the FDA reviewer, can be submitted with the report or included only in the archival copy of the submission.

7. Integrated Summary of Benefits and Risks

This section will be submitted in the format recommended in the clinical guidelines.

Item 11. Case Report Tabulations

Data tabulations by patient (Attachment 3) and collectively by parameter by study (Attachment 4) have been prepared for the two pivotal French studies. Based on the preference of the FDA reviewer, the submission can include tabulations presented in either or both formats.

Many of the other clinical studies in the submission include patient data listings as appendices to the full reports. These data listings will be submitted in this format as an integral part of the full report for a study.

Item 12. Case Report Forms

Case report forms have been requested from Roussel for patients in the two pivotal studies who died (none) or who experienced adverse events rated as "severe" whether or not this was due to the drugs. Case report forms for patients in other studies have not been requested by The Population Council and it is not known if the report forms are available. Please inform us if case report forms for the other studies are desired, and they will be requested. Because of the general design of the clinical studies which usually involves a single or double dosage schedule and a short per-patient study duration, it is very rare that a patient would discontinue the study. Thus we ask that you please also advise us of the desired criteria for specifying patients for whom case report forms are desired.

*** ***

We would appreciate any comments or suggestions which you may have regarding the proposed organization and content of our application. In addition, we would appreciate your response to the specific items mentioned previously:

- Is it acceptable to have Roussel provide a general confirmation that all investigators and facilities were appropriately qualified and that studies were performed in compliance with local ethical standards?

- Is it preferable that the data listings (seven volumes) for patients in the summary clinical laboratory report located in the integrated summary of safety be appended to the report or included only in the archival copy of the submission?

- Please specify the preferred format(s) (see Attachments 3 & 4) for the case report data tabulations.

- Are additional case report forms desired and by what criteria should patients be identified for whom the report forms should be requested from Roussel?

Sincerely yours,

C. Wayne Bardin, M.D.

Attachments (4)

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

The Population Council
Center for
iomedical Research

Mailed 6/8/95 /S/

N-130 Rx ORIGINAL

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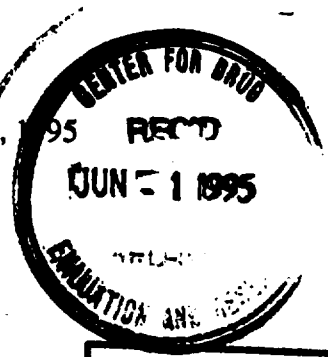
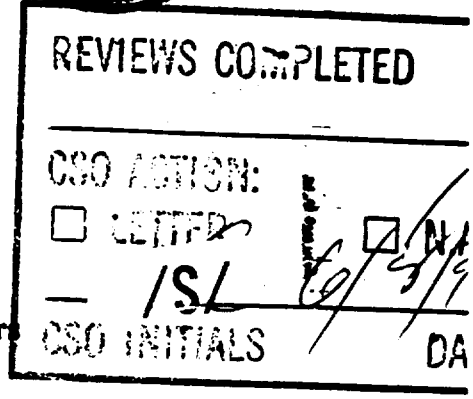
Telex: 238274 POBI UR



May 31, 1995

By FedEx

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



Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 130
Protocol Amendment - New Investigators

Dear —

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment - New Investigators

Enclosed are Statement of Investigator forms (Form FDA 1572) and curricula vitae for the following new investigators who will conduct clinical studies under Protocol 166A or 166B, as submitted October 27, 1994 - Submission Serial Number 105:

- Tyrone C. Malloy, M.D.
  Feminist Women's Health Center
  Atlanta, GA 30318
  (Protocol 166A)

Laszlo Sogor, M.D., Ph.D.
PRETERM
Cleveland, OH 44120
(Protocol 166B)

In addition, enclosed are revised Statements of Investigator for the following current investigators which provide for a revision in activities at the respective study sites. The

nature of the revision and date of submission and submission number of the most recent previous Statement of Investigator are indicated in parentheses for each study site.

Daniel R. Mishell, M.D.
University of Southern California
Los Angeles, CA 90033
(Nature of Revision - Addition of Subinvestigators

(Previous 1572 Submission - November 21, 1994/Submission 106)

Katharine Sheehan, M.D.
Planned Parenthood of San Diego and Riverside Counties
San Diego, CA 92108
(Nature of Revision - Addition of Clinical Laboratory -

(Previous 1572 Submission - February 9, 1995/Submission 116)

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

Sincerely yours,

C. Wayne Bardin

Enclosures

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
medical Research

1230 York Avenue
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Cable: Popblomed, New York
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N-129
IM, PC

noted
5/30/95
/S/

noted
/S/
5/31/95

May 18, 1995

REVIEWS COMPLETED
CSO ATTAIN:
☐ LETTER /S/ ☑ N.A.I. 5/24/95
CSO INITIALS DATE

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

Subject: **IND No. [redacted]; Mifepristone Tablets, 200 mg**
Submission Serial Number: 129
Information Amendment: Clinical
Protocol Amendment: Change in Protocol

Dear [redacted]

/S/

Information Amendment: Clinical

Enclosed, please find a further interim analysis of the data as of April 19, 1995 (Appendix I). This was conducted by [redacted] the contract research organization conducting the statistical analysis. These results are shown in Tables I and II. A total of 593 subjects has now been evaluated in Group 1, 297 in Group 2 and 177 in Group 3. The percentage success of medical termination of pregnancy with mifepristone and misoprostol was 95% in Group 1, 83% in Group 2 and 77% in Group 3 (Table I). By the Fisher's exact test, the success in Groups 2 and 3 was significantly less ($p < 0.001$) than in Group 1. There were, however, no statistical differences between Groups 2 and 3.

Table II analyzes the failure rate. It can be seen that continuing pregnancy, incomplete abortion and excessive bleeding increased progressively from Group 1 to Group 3. The incidences of continuing pregnancy and excessive bleeding were significantly increased in Groups 2 and 3 as compared to Group 1 ($p < 0.001$). The incomplete abortion rate was also greater in Groups 2 and 3 ($p < 0.05$) as compared to Group 1. Again, there were no differences between Groups 2 and 3. Table III indicates that these results have not changed since the initial analysis conducted in February 1995. As these cumulative data indicates, failure rate in Groups 1, 2 and 3 has ranged from 5-6%, 15-17% and 22-25% respectively. Table IV summarizes the adverse events which have been reported to your office.

CENTER FOR DRUG REC'D MAY 22 1995 HFD-510 EVALUATION AND RESEARCH

The Population Council

Protocol Amendment: Change in Protocol (Appendices II-IV)

Appendix II (Amendment No. 2 of Protocol 166 A and B).

This amendment is related to the measurements of SMA and hematological parameters and was approved by the IRB of The Population Council on 5 May 1995. SMA and hematology measurements will be performed prior to mifepristone administration and on day 15. It is planned to study a total of 216 subjects in 6 clinics. These clinics are those of Dr. Mitchell Creinin, University of Pittsburgh, School of Medicine; Dr. Lynn Borgatta, White Plains, New York; Dr. Tyrone C. Malloy, Atlanta, Georgia; Dr. Catherine L. Dean, St. Louis, Missouri; Dr., Laszlo Sogor from Cleveland, Ohio; and Dr. Rothenburg of Shrewburg, New Jersey. A total of 12 subjects in each group will be studied in the above clinics.

Appendix III (Amendment No. 3 of Protocol 166 A and B).

This amendment outlines the changes in the informed consent and describes the increased failure rates in Group 2 and 3, and thus increased need for surgical procedures with these groups. The amendment also gives a more complete description of the amount of bleeding. This amendment was approved by the IRB of The Population Council on 5 May 95.

Appendix IV (Revised Protocol 166A and B).

The changes of Amendments 2 and 3 are in bold print.

Should you have any queries or comments, please do not hesitate to contact me.

Sincerely yours,

C Wayne Bardin

C. Wayne Bardin

Enclosure

APPEARS THIS WAY
ON ORIGINAL

APPENDIX II

APPEARS THIS WAY
ON ORIGINAL

AMENDMENT #2

The protocol is being amended in order to determine if any changes occur in the blood chemistry or hematology parameters of subjects following the administration of mifepristone and/or misoprostol. Blood samples will be collected as outlined below.

The following additions to the protocol are indicated.

Blood samples will be collected prior to the administration of mifepristone at Visit 1 for the following: ***(page 10 of protocol)***

Chemistry Panel (4m*L*)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3m*L*)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count

Blood samples will again be collected at Visit 3 (Day 15) for the ***same measurements listed (page 13 of protocol)*** above.

A total of twelve (12) subjects per ***each*** group ***of amenorrhea duration,*** for a total of thirty-six (36) per center will be involved in these assessments at six (6) selected centers. ***Thus,*** a total of 216 subjects from the entire study population will participate.

The notification process (contact and telephone number) Section 7.1 is modified to remove ~~_____~~ and

insert: **Dr. Irving Spitz or Dr. C. Wayne Bardin**
The Population Council, Inc.
(800) 327-8730

AMENDMENT #2 (INFORMED CONSENT)

The informed consent text was modified to reflect the additional blood collections for chemistry and hematology. ***(on pages 30, 31, 32)***.

Section 2 Clinic Visits

1st paragraph

..... could endanger any future pregnancy. *I understand that I may be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood as well as determine the normal characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.* In order to.....

3rd paragraph

..... treatment has been effective. *I understand that I may again be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, and to determine the characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.* If the treatment.....

Section 4 Risks and Discomforts

1st paragraph, 1st sentence

..... for the tests at the first ***and third visits*** may be.....

APPEARS THIS WAY
ON ORIGINAL

AMENDMENT #3

The protocol is being amended in order to reflect the recent data indicating an increased need for surgical procedures in Groups 2 and 3.

The additions to the protocol and informed consent are indicated.

Informed Consent

Page 25 **add:**

Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women with amenorrhea of no more than 49 days before administration of mifepristone. In women with amenorrhea of 50 to 63 days before they received mifepristone, this new information suggests that as many as one in four may require some form of surgical procedure. There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. This excess bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.

Page 29 **delete:**

[ ]

Page 29 **add:**

Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone. In women whose first day of their last menstrual period occurred from 50 to 63 days before they received mifepristone, this new information suggests that as many as one in four may require some form of surgical procedure. There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.

Page 31: Section 2

Add:

I understand that the amount of bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period.

AMENDMENT #3 (con't)

Page 33: Section 4

Add:

I understand that uterine bleeding, similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period) and lasting at least one week, may be expected. **The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period.**

last paragraph

Add:

I understand that based on prior studies and recently obtained information, abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone.

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
medical Research

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

ORIGINAL

/S/

May 16, 1995

By FedEx

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

Subject: IND [redacted] · Mifepristone Tablets, 200 mg
Submission Serial Number: 128
Protocol Amendment - New Investigator

/S/

Dear [redacted]

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment - New Investigator

Enclosed is a Statement of Investigator form (Form FDA 1572) and curriculum vitae for the following new investigator who will conduct a clinical study under Protocol 166A, as submitted October 27, 1994 - Submission Serial Number 105:

Mitchell D. Creinin, M.D.
Magee-Woman's Hospital
Pittsburgh, PA 15213-3180

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

Sincerely yours,

for C. Wayne Bardin

Enclosures

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.
/S/ 7/24/95
CSO INITIALS DATE

noted 6/1/95 /S/

ORIGINAL

The Population Council

Center for medical Research

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NDA 19-827, 000

May 4, 1995

CENTER FOR DRUG REC'D MAY 08 1995 HFD-510 EVALUATION AND RESEARCH

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

Subject: **IND No. — Mifepristone Tablets, 200mg**
Submission Serial Number: 127
Response to FDA Request for Information on Protocol 166A and B, Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days

Dear —

As per your telephone request for information, enclosed please find two reports setting forth preliminary evaluations of the early results of the above study. It must be stressed that this represents an interim report rather than an in-depth statistical analysis of the case record forms. Also enclosed please find some relevant recent reprints from published literature. The reports and reprints are in the attached appendices described below.

/S/ 6/1/95

A total of 3 groups of subjects have been studied.
Group 1 have amenorrhea less than or equal to 49 days
Group 2 have amenorrhea between 50 and 56 days
Group 3 have amenorrhea between 57 and 63 days

The first report (Appendix I) was prepared by — the contract research organization assisting us with the analysis of the data from the French and the U.S. clinical trials. — analyzed a total of 641 subjects who had completed the study at the February cut-off date. There were 356 in Group 1, 184 in Group 2, and 101 in Group 3. The incidence of successful medical abortion in these three Groups was 95.2%, 82.6%, and 80.2%, respectively. Logistic analysis showed that Groups 2 and 3 had a significantly reduced success rate ($P<0.001$) compared to Group 1. Group 2 did not differ significantly from Group 3 (Fig. 1).

The second report (Appendix II) was prepared by — This is the organization which is monitoring the clinical study. — analyzed the reasons why subjects had an unsuccessful medical abortion following administration of mifepristone and misoprostol. Each clinic was requested to submit a short summary of all failures. This list is also included in Appendix II and forms the basis of the analysis. The number of subjects evaluated by — (Table 1) differs from the number analyzed by — due to a different cut-off date. However, the percentage of successful outcomes in Groups 1, 2, and 3 were similar, at 94.5%, 83.6%, and 77.3%, respectively. The rate of continuing pregnancy increased progressively from 1% in Group 1 to 6% and 9% in Groups 2 and 3, respectively.

REVIEWS COMPLETED
☐ LETTER ☐ MEMO
/S/ 6/1/95
CSO INITIALS DATE

The incidence of incomplete abortion was approximately the same in the three groups. Surgical intervention because of excessive bleeding increased from 1% in Group 1 to 5% and 9% in Groups 2 and 3, respectively. Included in instances of surgical intervention are 4 subjects who required blood transfusions and 5 who received intravenous fluids spread more or less equally among the three groups. The incidence of both excessive bleeding and continuing pregnancy was significantly greater in Groups 2 and 3 as compared to Group 1. With the results currently available, according to the one tailed Fisher's exact test, there were no statistical differences between Groups 2 and 3. Another analysis of our more recent data is under way, as there are now 1093 subjects who have completed the study (21 April 1995 cut-off date).

The results to date are similar to those from studies in the literature that are also enclosed in Appendices III - V. The study by Roger and Baird (Appendix III Contraception 40, 439, 1989) showed that blood loss was directly related to the length of gestation. In another study by Dr. Baird and colleagues (Appendix IV in press), it was reported that misoprostol (in a dose of 600 μg) is a safe alternative to the vaginal prostaglandin gemeprost, but there is a high incidence of ongoing pregnancies especially in women with amenorrhea of greater than 49 days. The incidence of complete abortion was 91.3% out of a total of 92 women with amenorrhea of 57-63 days as compared to 97.6% out of 83 women who received gemeprost as their prostaglandin.

McKinley, Thong and Baird (Human Reprod. 8, 1502, 1993, Appendix V) have shown that independent of the dose of mifepristone (600 or 200 mg) those subjects with amenorrhea of greater than 56 days have a lower complete abortion rate (89.1%) as compared to those women with amenorrhea of less than 49 days (97.5%) with a 600 μg dose of misoprostol. It is of note that the studies in Appendix IV and V used a higher dose than the dose used in the studies being conducted by the Council in the U.S. studies (i.e., 600 vs 400 μg).

[redacted]

In light of these results, we would recommend amending the informed consent for Protocol 166a and b. An IRB meeting tomorrow (5 May 1995) will consider an amended informed consent. This will be sent to your office when it is complete, along with a more recent analysis of our data.

All the patients for Group 1 have been enrolled. We continue to enroll in Groups 2 and 3.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin

CWB:sh

ORIGINAL

N-125
S2

The Population Council

Center for
medical Research

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

noted
4/28/95
/S/

April 19, 1995

BY FedEx

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

Subject: **IND No. ——— Mifepristone Tablets, 200mg**
Submission Serial Number: 125
IND Safety Report

Dear ———

Enclosed please find copies of FDA Form 3500 for adverse events reported to the Population Council for the above referenced study. These events were associated with

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

CWB:fia

/S/ 4/27/95

The Population Council
Center for
medical Research

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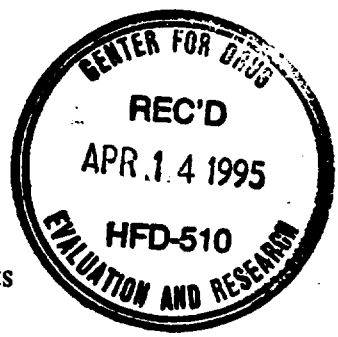
/S/

ORIGINAL

April 11, 1995



BY FedEx

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

/S/

Subject: **IND No. — Mifepristone Tablets, 200mg**
Submission Serial Number: 124
IND Safety Report

Dear —

Enclosed are MedWatch Forms for adverse events reported to the Population Council for the above referenced study. These involve — pages 01-04) and — (page 05).

If you require any additional information, please contact me.

Sincerely yours,

/Swk for

C. Wayne Bardin

CWB:fia

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
/S/ 4/20/95
CSO INITIALS DATE

MIF 004763

The Population Council
Center for
Biomedical Research

PI/IC
ORIGINAL

REVIEWS COMPLETED

CSO INITIALS February 9 1995

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2/15/95

/S/

Division of Metabolism and
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Center for Drug Evaluation and Research
Document Control Room 14B-03
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5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG REC'D FEB 10 1995 HFD-510 EVALUATION AND RESEARCH

Subject: IND —— **Mifepristone Tablets, 200 mg**
Submission Serial Number: 116
Protocol Amendment- **Additional Information on Investigators**
Information Amendment- **Chemistry, Manufacturing and Controls**

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend the application to provide information identifying the investigators participating in the "A" or "B" versions of Protocol 166 and to provide additional chemistry, manufacturing and controls information on the investigational drug supplies used in the study.

1. Investigators Participating in "A" or "B" Versions of Protocol 166

In Submission 105 (October 27, 1994) which forwarded the present version of Protocol 166A, we discussed that a parallel study is being conducted simultaneously under Protocol 166B which is identical to Protocol 166A. Table One below identifies the investigators currently participating in the two studies.

Statements of Investigator (Form FDA 1572) and curricula vitae have been previously submitted for each of the investigators in the table; however, for the four investigators listed below, it was not indicated on their respective Statements of Investigator that they were participating under Protocol 166B. Revised Statements of Investigator

Table One

Investigators Participating in Protocols 166A and 166B

Protocol 166A	Protocol 166B
P. Blumenthal, MD Baltimore, MD	M. Nichols, MD Portland, OR
S. Haskell, DO Des Moines, IA	[redacted]
D. Mishell, MD Los Angeles, CA	A. Poindexter, MD Houston, TX
S. Poppema, MD Seattle, WA	K. Sheehan, MD San Diego, CA
J. Tyson, MD Williston, VT	P. Vargas, MD Denver, CO
	C. Westhoff, MD New York, NY

documents have been obtained from the investigators and are included in this submission as Attachment A .

A. Poindexter, MD
Houston, TX

P. Vargas, MD
Denver, CO

K. Sheehan, MD
San Diego, CA

C. Westhoff, MD
New York, NY

2. Chemistry, Manufacturing and Controls Information

Attachment B contains updated information on manufacture and control procedures recently received from Roussel Uclaf for the investigational drug supplies provided to us by that company. As stated in the foreword to the document, the update includes information on the manufacture of the smaller batch size —— tablets) of the investigational supplies, product packaging, updated control procedures for the drug product and drug substance, and stability results.

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

Sincerely yours,

for C. Wayne Bardin

APPEARS THIS WAY
ON ORIGINAL

Attachments

The Population Council
Center for
Biomedical Research

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

ORIGINAL
132
#52

[redacted]

noted
6/14/95
/S/

June 7, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN - 9 1995
HFD-510

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By FedEx

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

19 June 95
/S/

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 132
IND Safety Reports

Dear [redacted]

Enclosed please find a copy of FDA Form 3500 for adverse events reported to the Population Council for the above referenced study. These events were associated [redacted] (page 01, also reported in a telephone report on June 2, 1995); [redacted] (pages 02 and 03); [redacted] (pages 04 and 05); and [redacted] (page 06).

If you require any additional information, please contact me.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin

Enclosures

REVIEWS COMPLETED
CSO ACTION:
☐ LET /S/ ☒ N.A.
6/19/95

MIF 004767

ne Population Council

nter for
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1230 York Avenue
New York, New York 10021
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N-133 S2

[redacted]

ORIGINAL

Noted
6/19/95
/S/

June 13, 1995

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JUN 14 1995
HFD-510
EVALUATION AND RESEARCH

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

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 133
IND Safety Report

19 /S/ Jun 95

Dear [redacted]

Enclosed please find a copy of FDA Form 3500 for an adverse event reported to The Population Council for the above referenced study. This event was associated [redacted]

If you require any additional information, please contact me.

Sincerely yours,

/S/ for

C. Wayne Bardin

Enclosure

REVIEWS COMPLETED
CSO ACTION:
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/S/ 6/19/95
CSO INITIALS

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
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N1 134 PI

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June 27, 1995

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/S/ 7/10/95
☐ N.A.I.
CSO INITIALS DATE

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

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 134
Protocol Amendment - New Investigator

Dear [redacted]

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment - New Investigator

Enclosed is a Statement of Investigator Form (Form FDA 1572) and curriculum vitae for the following new investigator who will conduct a clinical study under Protocol 166A, as submitted May 18, 1995 - Submission Serial Number 129:

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Eugene Rothenberg, M.D.
Planned Parenthood of Central New Jersey
Shrewsbury, NJ 07702

In addition, enclosed are revised Statements of Investigator Forms for the following current investigators to include the addition of a clinical laboratory; [redacted]; for the measurements of SMA and hematological parameters in accordance with Amendment No. 2 to Protocol 166A,B submitted May 18, 1995 - Submission Number 129. The date of submission and submission number of the most recent previous Statement of Investigator Form are indicated in parentheses for each study site.

Lynn Borgatta, M.D., M.P.H.
Planned Parenthood of Westchester/Rockland, Inc.
White Plains, NY 10607
(Previous 1572 Submission - May 2, 1995/Submission 126)

Mitchell D. Creinin, M.D.
Magee-Women's Hospital
Pittsburgh, PA 15213-3180
(Previous 1572 Submission - May 16, 1995/Submission 128)

Catherine L. Dean, M.D., M.P.H.
Obstetric and Gynecologic Diagnosis & Consultation
Florissant, MO 63031
(Previous 1572 Submission - May 2, 1995/Submission 126)

Tyrone Malloy, M.D.
Feminist Women's Health Center
Atlanta, GA 30318
(Previous 1572 Submission - May 31, 1995/Submission 130)

Laszlo Sogor, M.D., Ph.D.
PRETERM
Cleveland, OH 44120
(Previous 1572 Submission - May 31, 1995/Submission 130)

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

Sincerely yours,

CW Bardin

C. Wayne Bardin

Enclosures

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ORIGINAL

The Population Council

Center for
medical Research

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

July 18, 1995

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

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 136
IND Safety Report

Dear [redacted]

Enclosed please find FDA forms 3500 regarding two adverse events reported to the Population Council for the above referenced study. These events occurred [redacted]

Please note that Submission Serial Number 135 has been assigned to a submission that will be submitted directly to the IND by Roussel Uclaf.

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

Sincerely yours,

C. Wayne Bardin

Enclosures

REVIEWS COMPLETED
CSO ACTION:
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/S/ 7/25/95
CSO INITIALS DATE

MIF 004771

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/S/ 8/2/95

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HFD-510

July 25, 1995

FedEx

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

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 138
IND Safety Report

Dear —

Enclosed please find an FDA form 3500 regarding an adverse event reported to the Population Council for the above referenced study. This event occurred — at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

REVIEW COMPLETED
CSO ACTION:
☐ IND /S/ ☐ N.A.I.
CSO INITIALS DATE

Population Council
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New York, New York 10021
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July 28, 1995

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

Noted 8/3/95 /S/

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 139
IND Safety Report

Dear ———

Enclosed please find an FDA Form 3500 regarding an adverse event reported to you in a telephone report on July 28, 1995 by Fred Schmidt of the Population Council for the above referenced study. This event occurred ——— and ——— at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

APPEARS THIS WAY
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[redacted] COMPLETED

CSO [redacted]:

☐ [redacted] ☒ N.A.

/S/ 8/3/95

CSO INITIALS DATE

ORIGINAL

e Population Council

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nedical Research

1230 York Avenue
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August 3, 1995

By FedEx

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

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 140
Information Amendment - Pharmacology/Toxicology
- Clinical

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information provided to us by Roussel Uclaf, as follows:

1. **Pharmacology/Toxicology Information - Reproduction Study (Appendix 1)**

Enclosed is a new reproduction study entitled:

"Study of the Development and Fertility of Young Rats Treated Subcutaneously with a Single Injection on Day 1 after Birth"

In the study, mifepristone was administered subcutaneously at doses of 0, 1, 10 and 100 mg/kg to young male and female rats on the first day after birth to assess the effect of the drug on physical development, puberty and the reproductive function. Under the conditions of the study, mifepristone was not seen to affect the general development of the animals. A tendency to early onset of puberty was apparent in females treated with 100 mg/kg; no effect was noted in males. Reproductive function was regarded as normal in both sexes.

2. **Clinical Information**

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I.
/S/ 7/12/96
CSO INITIALS DATE

MIF 004774

A. **Mifepristone Safety Report (June 1993) - For the Period of January 1, 1991 - December 31, 1992 (Appendix 2, pages 128-190)**

This enclosed 1993 report summarizes safety experience from spontaneous reports of adverse events received by Roussel Uclaf and adverse events reported in clinical studies. It is our understanding that the report is presently being updated by Roussel Uclaf and a more current report will be forwarded when available.

Appended to the above safety report are printouts received from Roussel Uclaf as follows:

- spontaneous reports and reports from a Phase IV study "English PMS" received by the company in the period from January 1, 1993 - October 12, 1994. **(Appendix 2.1, pages 191-194)**

- individual "quarterly" listings of the adverse events in international clinical studies for the period from June 1, 1993 to June 30, 1995. **(Appendix 2.2, pages 195-306)**

Please note that the Population Council has also received from Roussel Uclaf a number of individual adverse reaction reports the majority of which are thought to be summarized in the above enclosed quarterly listings. These reports are now being analyzed. The total body of information received is considered not to completely cover the full postmarketing and investigational experience. Additional information has been requested and will be submitted when available.

B. **Report (June 7, 1995) from Roussel Uclaf on "Tolerance of RU 486 during US Studies" (Appendix 3, pages 307-312)**

This document summarizes safety information available to Roussel Uclaf on clinical studies performed in the US

C. **Report (July 6, 1995) from Roussel Uclaf on "Relevant Information Collected on Ongoing Pregnancies after the Intake of Mifepristone for Early Pregnancy Termination (1st Trimester)" (Appendix 4, pages 313-317)**

This document summarizes information obtained by Roussel Uclaf on the subject.

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

Sincerely yours,

C. Wayne Bardin

Enclosures

for CW Bardin

e Population Council

ter for
nedical Research

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

Dated
8/10/95
/S/ August 4, 1995

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By FedEx

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

CENTER FOR DRUG
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HFD-510
EVALUATION AND RESEARCH

Subject: IND ——— **Mifepristone Tablets, 200 mg**
Submission Serial Number: 141
IND Safety Report

Dear ———

Enclosed please find an FDA Form 3500 regarding an adverse event reported to you in a telephone report on August 3, 1995 for the above referenced study. This event occurred at ——— at that site.

/S/
10 Aug 95

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

Sincerely yours,

C. Wayne Bardin

/S/ C Wayne Bardin

Enclosure

APPEARS THIS WAY
ON ORIGINAL

REVIEW COMPLETED
/S/ 9/10/96 N.A.I.
DATE

The Population Council
Center for
Biomedical Research

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

August 4, 1995

By FedEx

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

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 141
IND Safety Report

Dear ——

Enclosed please find an FDA Form 3500 regarding an adverse event reported to you in a telephone report on August 3, 1995 for the above referenced study. This event occurred at —— at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

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ON ORIGINAL

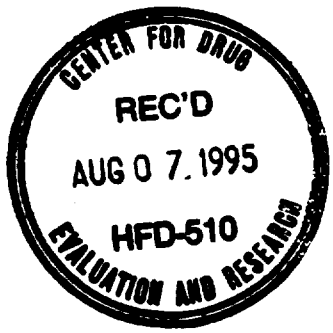
The Population Council

Center for
Biomedical Research

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

August 4, 1995

By FedEx



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

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 141
IND Safety Report

Dear ———

Enclosed please find an FDA Form 3500 regarding an adverse event reported to you in a telephone report on August 3, 1995 for the above referenced study. This event occurred at ——— at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

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ON ORIGINAL

The Population Council

Center for
Biomedical Research

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1230 York Avenue
New York, New York 10021
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Dated
8/14/95
/S/

August 7, 1995

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

Subject: IND —— **Mifepristone Tablets, 200 mg**
Submission Serial Number: 142
Protocol Amendment-Revised Statement of Investigator's Forms

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

Protocol Amendment - Revised Statement of Investigator's Forms

Enclosed are revised Statement of Investigator Forms (FDA 1572) for the following current investigators which provide for an addition of a subinvestigator and/or an on site clinical laboratory at the respective study sites. The nature of the revision and date of submission and submission number of the most recent previous Statement of Investigator Form are indicated in parentheses for each study site.

—— Lynn Borgatta, M.D., M.P.H.
Planned Parenthood of Westchester/Rockland, Inc.
White Plains, NY 10607
(Nature of Revision: Addition of Subinvestigator - ——
—— and Addition of Clinical Laboratory - on site laboratory at Planned Parenthood)
(Previous 1572 Submission - June 27, 1995/Submission 134)

Judy Tyson, M.D.
Planned Parenthood of Northern New England
51 Talcott Rd., #1
Williston, VT 05495
(Nature of Revision: Addition of Subinvestigator -
and Addition of Clinical Laboratory - on site laboratory

FORM SUBMITTED
ACTION:
LETTER
/S/
N.A.I.
INITIALS
DATE

The Population Council

at Planned Parenthood)
(Previous 1572 Submission - November 21, 1994/Submission 106)

Carolyn Westhoff, M.D.
Department of Obstetrics and Gynecology
Columbia University
630 West 168th Street
NY, NY 10032
(Nature of Revision: Addition of Clinical Laboratory -

(Previous 1572 Submission - February 9, 1995/Submission 116)

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

Sincerely yours,

for C. W. Bardin

C. Wayne Bardin

Enclosures

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nedical Research

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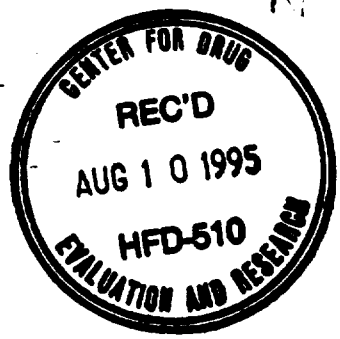

/S/

August 9, 1995

By FedEx

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

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 143
IND Safety Report

Dear ———

Enclosed please find FDA Forms 3500 regarding two adverse events reported to you in a telephone report on August 8, 1995 for the above referenced study. These events occurred at ——— at that site.

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

Sincerely yours,

/S/

C. Wayne Bardin

Enclosure

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CSO ACTION:
☐ LETTER /S/ ☒ N.A.
CSO INITIALS 8/16/95 DATE

MIF 004781

ORIGINAL

Population Council

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New York, New York 10021
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August 10, 1995

By FedEx

REVIEWS COMPLETED

CSO ACTION:
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/S/ 8/10/95
CSO INITIALS DATE

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

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 144
IND Safety Report

Noted /S/ 8/17/95

Dear —

Enclosed please find a follow-up FDA Form 3500 regarding an adverse event initially reported on August 9, 1995 in Submission Number 143 (page 02) for the above referenced study. This event occurred —

at that site.

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

Sincerely yours,

/Signature for CW Bardin

C. Wayne Bardin

Enclosure

ORIGINAL

N 145
S2

The Population Council
Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
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8/21/95
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August 15, 1995

By FedEx

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

/S/ 8/21/95

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 145
IND Safety Report

Dear ——

Enclosed please find FDA Forms 3500 regarding two adverse events reported to the Population Council for the above referenced study. These events occurred at —— at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
/S/ 8/21/95
CSO INITIALS DATE

MIF 004783

Population Council
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N.146
S2

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/S/

August 25, 1995

By FedEx

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

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 146
IND Safety Report

Dear ———

Enclosed please find a FDA Form 3500 regarding an adverse event reported to the Population Council for the above referenced study. This event occurred at ——— at that site.

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

Sincerely yours,

C. Wayne Bardin

Enclosure

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ NAI

/S/ 9/6/95

CSO INITIALS DATE

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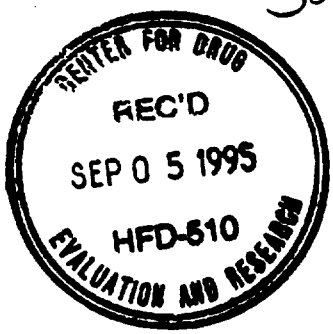
ORIGINAL
147 SA



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Telex: 238274 POBI UR

noted 9/14/95
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/S/
9/5/95

September 1, 1995

By FedEx

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

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 147
IND Safety Report

Dear —

Enclosed please find two FDA Forms 3500 regarding an adverse event reported to the Population Council for the above referenced study. This event occurred at — and — at that site. Please note that both froms pertain to the same patient. The patient came to the ER twice on August 26, 1995.

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

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin

Enclosure

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER /S/ ☒ N.A.I. 9/6/95
CSO INITIALS DATE

The Population Council
Center for
medical Research

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Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

mailed
10/2/95
/S/

September 21, 1995

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

/S/

Subject: IND [redacted] Mifepristone Tablets, 200mg
Submission Serial #149
IND Safety Report

Dear [redacted]

Enclosed please find an FDA form 3500 regarding an adverse event reported to the Population Council for the above referenced study. This event occurred at [redacted] at that site.

As always if you have questions, please feel free to contact me.

Sincerely,

C. Wayne Bardin
Director, Vice President

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER
/S/ 10/2/95
☒ N.A.I.
CSO INITIALS DATE

The Population Council

Center for
Biomedical Research

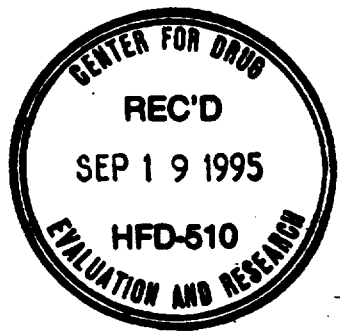
1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

ORIGINAL
N148
JT,JM

Noted 9/22/95 /S/

September 18, 1995

/S/ 7/12/96



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

Subject: IND **Mifepristone Tablets, 200 mg**
Submission Serial Number: 148
Information Amendment- Pharmacology/Toxicology
Clinical

Dear

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our IND with new information provided to us by Roussel Uclaf, as follows:

1. **Pharmacology/Toxicology Information**

Enclosed are reports of four new studies as described below:

Study of the Destructive Potential of RU 38486 on Rat Liver Cytochromes P-450 -- (Study Reference Number: 92/3980/TX) -- (Appendix 1)

In this *in vitro* study, mifepristone caused slight but significant destruction of cytochromes P-450 in dexamethasone-induced rat liver microsomes. Demethylation of the compound appeared to involve the family IIIA enzyme and to result in its inactivation. The results of this study suggest the possibility

of an influence on the metabolism of other substrates of the enzyme. Because family IIIA is predominant in man, this potential effect should be considered in therapeutic drug combinations involving mifepristone.

Effects on the Development of Rat Embryos in Culture (7.2, 14.4, 21.6 and 28.8 µg/ml) -- (Study Reference Number: 92/4263/TX) -- (Appendix 2)

To investigate the effect on the *in vitro* growth and development of rat embryos explanted on Day 9.5 of gestation, mifepristone was added to cultures of the embryos in amounts equal to 3, 6, 9 and 12 times a standard concentration of 2.4 µg/ml. Cultures were prepared with and without a metabolic activation system (S-9 mix). In the absence of the activation system, no lethal or dysmorphogenic activity was observed on the embryos. In the presence of the activation system, mifepristone displayed a tendency to cause morphological abnormalities and modifications of developmental parameters. These observations were considered to indicate a tendency to a teratogenic potential.

^{3}H-RU 38486 - Study of Transplacental Passage in the Rat -- (Study Reference Number: 92/4182/TX) -- (Appendix 3)

Following a single oral dose of 100 mg/kg of tritiated mifepristone given to pregnant rats 24 hours before the presumed date of parturition, no effect was seen on the dams or on their offspring. Mifepristone crossed the placenta in that radioactivity and the compound were found in plasma of the offspring.

Development and Fertility Study of Offspring from Female Rats Treated Orally with a Single Dose on Day 21 of Gestation (1, 10, 100 mg/kg) -- (Study Reference Number: 92/4098/TX) -- (Appendix 4)

Mifepristone was administered orally in single doses of 0, 1, 10 or 100 mg/kg to pregnant rats on Day 21 of gestation to evaluate the effect of the compound on reproductive function in the offspring. No significant effect was observed on the treated dams, on the development and behavior of the F1 offspring and on the reproductive function of the F1 offspring.

2. **Clinical Information**

Mifepristone International Safety Report (July 1995) -- Periodic Update - For the Period of January 1, 1993-May 31, 1995 -- (Appendix 5)

This report summarizes worldwide safety information received by Roussel Uclaf from all sources (post-marketing studies, spontaneous notifications, literature, and clinical trials) during the time period covered. The report is an update of the previous safety report which covered the period of January 1, 1991 - December 31, 1992 and which was included in Submission 140 to this IND on August 3, 1995.

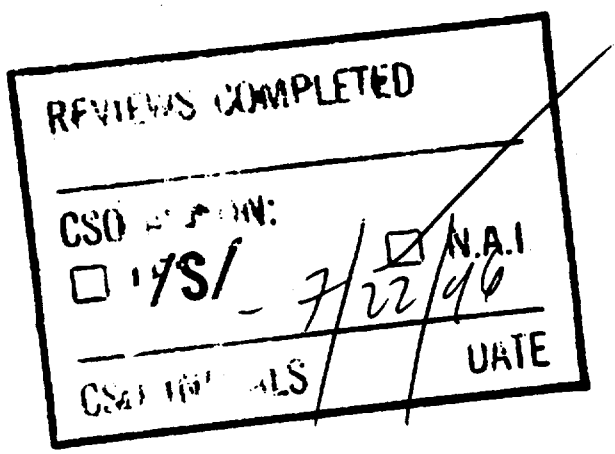
Please contact me should there be any questions or comments regarding the above information.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin, M.D.
Director

Enclosures



The Population Council
Center for
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Telex: 238274 POBI UR

noted 10/1/95 /S/ ORIGINAL

September 26, 1995

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

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D SEP 29 1995 HFD-510

Subject: IND —— **Mifepristone Tablets, 200 mg**
Submission Serial Number: 150
Annual Report

/S/

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion.

Please find enclosed our Annual Report which describes recent activities in our development program with mifepristone. Our last report was submitted on July 15, 1993 and this current report is intended to cover the period of time since that report up to July 31, 1995. In the time from the submission of our last report until August 1994, The Population Council sponsored no investigational activities with the drug. With our IND Submission Number 100 on August 3, 1994, we initiated our present major clinical development program which is outlined in this report.

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

Sincerely yours,

C Wayne Bardin

C. Wayne Bardin, M.D.
Director

Enclosure

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

312.33 (b) Summary Information. Information obtained during the previous year's clinical and nonclinical investigations, including:

(2) A summary of all IND safety reports submitted during the past year.

The following table summarizes all IND safety reports submitted as of July 31, 1995.

Protocols 166A/B
IND Safety Reports Submitted to FDA

As of July 31, 1995

IND Submission (Number - Date)	Patient Identification	Investigator	Adverse Experience
107 - 11/21/94	1	Vargas	Hemorrhage
108 - 12/01/94	036	Haskell	Fainting, vomiting, dehydration, hemorrhage, nausea
	033	Haskell	Nausea, dehydration, vomiting, diarrhea
109 - 12/07/94	027	Haskell	Hemorrhage
	042	Haskell	Hemorrhage
	1	Vargas	F/U information on report in S/107 above
110 - 12/20/94		Mishell	Dizziness, headache, hypotension, tachycardia, hemorrhage
113 - 01/18/95	015	Nichols	Hemorrhage
	012	Nichols	Hemorrhage
	01 061	Mishell	Hemorrhage, weakness, nausea
	076	Haskell	Nausea, vomiting, hemorrhage
	033	Poppema	Hemorrhage, syncope

IND Safety Reports Submitted in the Reporting Period (Cont.)

As of July 31, 1995

IND Submission (Number - Date)	Patient Identification	Investigator	Adverse Experience
114 - 01/23/95	022	Nichols	Hemorrhage
	050	Poppema	Hemorrhage, hypotension
115 - 02/07/95	009	Sheehan	Hemorrhage, dizziness, syncope
118 - 02/15/95	01 062	Mishell	Hemorrhage
	01 107	Mishell	Weakness, dizziness, nausea, vomiting
	01 114	Mishell	Hemorrhage
	01 123	Mishell	Headache, dizziness, hemorrhage
	037	Tyson	Hemorrhage
119 - 02/17/95	01 109	Mishell	Hemorrhage
	01 109	Mishell	Endometritis
	01 116	Mishell	Chest pain
120 - 03/03/95	048	Poppema	Hemorrhage, tachycardia
121 - 03/06/95	076	Poppema	Hemorrhage
122 - 03/10/95	60	Westhoff	Hemorrhage, hypotension, tachycardia
123 - 03/13/95	17	[redacted]	Hemorrhage, hypotension
	70	Haskell	Gunshot injury (hospitalization)
124 - 04/11/95	30	[redacted]	Hemorrhage, syncope, hypotension, tachycardia
	32	[redacted]	Vasovagal reaction
	35	[redacted]	Hemorrhage
	37	[redacted]	Dizziness, shortness of breath, hemorrhage
	081	Sheehan	Hemorrhage, syncope
125 - 04/19/95	158	Haskell	Hemorrhage, weakness, fatigue
	01 159	Mishell	Hemorrhage

IND Safety Reports Submitted in the Reporting Period (Cont.)

As of July 31, 1995

IND Submission (Number - Date)	Patient Identification	Investigator	Adverse Experience
132 - 06/07/95	036	Dean	Pneumonia
	012	Sogor	Hemorrhage, weakness, faintness
	028	Tyson	Hemorrhage, dizziness, weakness
	075	Tyson	Nausea, dizziness
	004	Creinin	Hemorrhage
133 - 06/13/95	027	Creinin	Vomiting, hemorrhage, lightheadedness
136 - 07/18/95	071	[redacted]	Vomiting, hemorrhage, dizziness
	030	Creinin	Hemorrhage
138 - 07/25/95	033	Creinin	Hemorrhage
139 - 07/28/95	063	Creinin	Anxiety attack, threatened suicide, depression

APPEARS THIS WAY

ROUSSEL UCLAF

Drug Regulatory Affairs
Health Care Division

/TN - 95.463

October 27, 1995

Division of Metabolism and Products HFD-510
Office of Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857 - USA

Mifepristone (RU 38486) : IND
Amendment - CMC section

Dear

On behalf of the Population Council, please find enclosed the amendment to IND concerning the CMC section.

Please let us know if you need any other information.

Sincerely,

cc : Population Council

102, route de Noisy 93235 Romainville Cedex
Tél. + 33 (1) 49 91 49 91 Fax. + 33 (1) 49 91 30 94 - + 33 (1) 49 91 32 96
SIRET 542 008 081 00052 00045

ORIGINAL

MEMO OF TELEPHONE CONVERSATION

FEB 23 1996

I contacted Catherine Euvard today and stated that it was my understanding that Roussel was planning to respond to the list of questions FAXed to them earlier. She stated that Roussel and the Pop. Council would have to discuss this because Roussel did not want to do anymore work. I said that it was my understanding that several of the questions were questions that only Roussel could answer, but that I did not want to get into the middle of something that Roussel and the Pop. Council had to work out. I stated that the reason I had called was to give them the name of someone who would help them to decide what needed to be put into their EA section. I then gave her [redacted] name and phone number.

Dr. Euvard stated that she did not understand why they had to submit an EA when they were not going to ever supply drug to the U.S. I told her that everyone understood that Roussel would not be supplying drug, however an NDA had to be complete in order for it to be reviewed and because they were listed in the IND as the manufacturer, they would have to submit all of the pieces.

Dr. Euvard said that she was not the one that made decisions, and did not understand all of the nuances, but that she would give the name and number of [redacted] to Joe Scheeren, who was not expected in until Friday, and he would get in touch with [redacted]

APPEARS THIS WAY
ON ORIGINAL

DATE Februayr 12, 1996

NDA/IND NUMBER
IND [redacted]

INITIATED BY
[redacted]
HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Catherine Euvard

TELEPHONE
9-011-33-1-4991-4252
FAX 9-011-33-1-4991-3119

cc:
uterine acting
HFD-510/ [redacted]

DIVISION HFD-510

ORIGINAL

MEMO OF TELEPHONE CONVERSATION

ORIGINAL FEB 23 1996

Dr. [redacted] called to clarify the contact made with Dr. Euvard on February 12, 1996. I said that I had called to give Roussel the name and number of a contact that could help them determine what they would have to provide, and what they would not have to provide in their EA section. I then gave the name of [redacted] again. Dr. [redacted] said that he had hoped that they would not have to have an EA section. I told him it had been decided in a higher level meeting that they would, but that this woman would be helping them.

Dr. [redacted] said that they only have [redacted] left of the drug substance that went into the making of the drug. I told him that I had given that question to [redacted] and he had said that it would be alright if the drug substance came from a different lot. However, [redacted] wanted to remind them that if reference standards were used in the methods of manufacture, that we would require the standards as well. I stated that I believed that this was a routine request, and should not be a surprise. Dr. [redacted] agreed that this was a standard request and that he would work on it. He also stated that Roussel was planning to respond to all the questions on our list.

I told him that I had one more concern. I noted that Roussel very obviously wanted to work through the Population Council to answer questions, and not directly with the FDA, and said that I understood this. However I requested that they think about how they wanted to answer any other chemistry questions that might come up during review if the Population Council was to be blind to the CMC section. I pointed out that the review that the reviewing chemist had done had been cursory, and meant only to cover obvious deficiencies. Dr. [redacted] said that Roussel was going to have an internal meeting to discuss these things, and that he would bring up that point.

Discussion ended at that point.

DATE February 14, 1996

NDA/IND NUMBER
IND [redacted]

INITIATED BY
Dr. [redacted]

HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. [redacted]

TELEPHONE
9-011-33-1-4991-4252

FAX
9-011-33-1-4991-3113

cc:
Uterine Acting
HFD-510/ [redacted]

DIVISION HFD-510

ORIGINAL

MEMO OF TELEPHONE CONVERSATION

FEB 23 1996

Following my telephone conversation with Dr. Euvard I called [redacted] to let her know that Dr. [redacted] would be calling probably either the end of this week or the following week. I outlined the CMC problem, and [redacted] decision to have [redacted] get involved. I requested that if Dr. [redacted] had not contacted her by the end of next week, that she give me a call.

[redacted] said that she was going on vacation soon, but would be in the office on Monday. She also stated that if she had not heard from anyone by the 20th of February she would call me.

APPEARS THIS WAY
ON ORIGINAL

DATE February 12, 1996

NDA/IND NUMBER
[redacted]

INITIATED BY
[redacted]
HFD-510

PRODUCT NAME
Mifipristone

SPONSOR'S NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
[redacted]

TELEPHONE
[redacted]

cc:
Uterine Acting
HFD-510, [redacted]

DIVISION HFD-510

The Population Council
Center for
medical Research

ORIGINAL
150

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

Clinical Investigation section is accepted: /S/ 12/21/95

December 18, 1995

CENTER FOR DRUG
REC'D
DEC 1.9 1995
HFD-510
EVALUATION AND RESEARCH

not filed /S/ 3-14-96

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

Subject: IND **Mifepristone Tablets, 200 mg**
Submission Serial Number: 157
General Correspondence

Dear

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. We also refer to the recent meeting on October 24, 1995 with members of your division to discuss planning for the submission of a New Drug Application.

In our meeting, we discussed the general format and organization of our planned application. We are now heavily involved in the preparation of the submission and several issues have arisen on which we would appreciate your consideration.

1. **Format of NDA Item 6 -- Human Pharmacokinetics and Bioavailability Section**

In the meeting, we were advised by the reviewer of this section of a desired format for the presentation of information in the section and we were provided with a copy of a guideline outlining the desired format. This new guideline covers basically the same informational contents as the "Guideline for the Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application" (2/ er, the new guidelines presents a different format for presentation of the informa ortunately we have already completed preparation of the NDA section using the format in the 1987 guideline.

Enclosed is a copy of the draft table of contents for the section as it is now prepared along with several examples of the draft summary tables used in the document (Appendix I). We would appreciate your consideration as to whether it will be permissible for us to submit the section in the current format as it is now prepared.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I.
/S/ 2-27-96
CSO INITIALS

2. Format of NDA Items 8 and 10 -- Clinical Data Section and Statisical Section

In the meeting, we also stated that we would submit the enclosed copy of the draft table of contents for the clinical section to assure that the section includes an appropriate organization of the documentation for the convenience of review (Appendix II). We further discussed that the clinical section would consist of the two pivotal studies performed by Roussel Uclaf along with many other studies performed by the manufacturer. The two pivotal studies and almost all the other studies are regarded as historically controlled.

Because of the controlled nature of the studies, we normally would include in the statistical section a complete copy of the "Controlled Clinical Studies" portion of the clinical section so that both sections would include full reports of all controlled studies. However, because of the emphasis placed on the pivotal studies and in view of the size (approximately 25 volumes) of the remaining studies, we propose that the "Controlled Clinical Studies" portion of the statistical section include full reports for only the two pivotal studies. Synopses would be included in the section for the remaining controlled studies.

We would appreciate any comments you may have on the table of contents for the clinical section and your acceptance of our proposal for the content of the statistical section.

Sincerely yours,

Ann Robbins

for C. Wayne Bardin, M.D.
Vice President

Enclosures:

Appendix I: Table of Contents and Summary Tables for Human Pharmacokinetics and Bioavailability Section

Appendix II: Table of Contents for Clinical Data Section

APPEARS THIS WAY
ON ORIGINAL

e Population Council
ter for
nedical Research

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

ORIGINAL

N156 p1

12/18/95 /S/

December 4, 1995

By FedEx

not rec'd /S/ 12-20-95

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 0 5 1995
HFD-510

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 156
Protocol Amendment-Revised Statement of Investigator Form

N/A /S/

Dear ———

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with revised information, as follows:

Protocol Amendment - Revised Statement of Investigator Form

Enclosed is a revised Statement of Investigator Form (FDA 1572) for the following investigator which provides for an addition of an on site clinical laboratory. The date of submission and submission number of the most recent previous Statement of Investigator Form is indicated in parenthesis for this study site.

Tyrone Malloy, M.D.
Feminist Women's Health Center
Atlanta, GA 30318
(Previous 1572 Submission - June 27, 1995/Submission 134)

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

Sincerely yours,

Ann Robbins for
C. Wayne Bardin

Enclosure

MIF 004800