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

Communications with the FDA regarding review of application

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

Decisions made:

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

Action Items:

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

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:
Original NDA 20-687
HFD-580/DivFile
HFD-580/
HFD-5
HFD-1

draftec
concur
final: I

TELECONFERENCE MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: May 31, 2000 **Time:** 9:00-11:00 am **Location:** Parklawn; 17B-43

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

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Labeling Meeting

Meeting Chair:

Meeting Recorder:

FDA Attendees:

, Office of Drug Evaluation III (ODEIII, HFD-103)
Division of Reproductive and Urologic Drug Products
(DRUDP, HFD-580)
DP (HFD-580)
, DRUDP (HFD-580)
Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To continue discussions regarding the proposed distribution system and to begin labeling edits.

Background: This NDA was originally submitted on March 14, 1996 receiving an approvable action on September 18, 1996. This application had a complete response dated August 18, 1999 and received another approvable action on February 18, 2000. The sponsor submitted this resubmission dated March 30, 2000 as a complete response.

Discussion:

- teleconference held with sponsor on May 19, sponsor to submit proposed physician qualifications, provider auditable criteria (no time frame given); sponsor also to submit Phase 4 summary protocols by August 1, 2000
- Proposed Restricted Distribution System:

Decisions Made:

Action Items:

- to schedule a T-con between and for 6/1/00 and the sponsor to discuss provider qualifications necessary for restricted distribution system, and to relay that we will have major label revisions to present to them within 2 weeks

Minutes Preparer **Concurrence, Chair**

Note: Teleconference with sponsor on 6/1/00; minutes faxed to sponsor on 6/5/00.

cc:
Original NDA
HFD-580/DivFile
HFD-580
HFD-580
HFD-102
Drafted: May 31 2000
Initialed:
Final June 8, 2000

MEETING MINUTES

Teleconference Minutes

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

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

Sponsor: Population Council

Type of Meeting: Advice

Meeting Chair:

External Lead:

Meeting Recorder:

FDA Attendees:

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

External Attendees:

The Danco Group
Sandra Arnold, Population Council
Nancy Buc, Buc and Beardsley

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

Discussion:

Phase 4 protocols

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

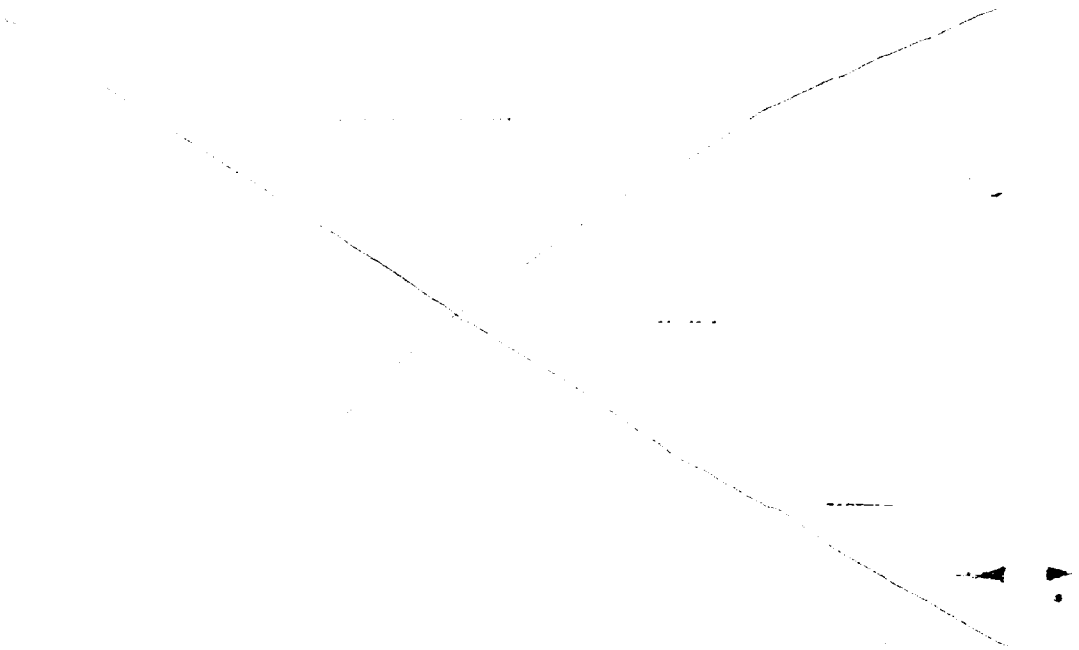
Restricted Distribution

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

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

Proposed Restricted Distribution System for NDA 20-687

Labeling recommendations



Decisions made:

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

Action Items:

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

Minutes Preparer **Concurrence, Chair**

cc:
Original NDA 20-687
HFD-580/DivFile
HFD-580/
HFD-58(
HFD-10

drafted: .1.00
concurrence: 5.2.00
final 6.2.00

TELECONFERENCE MINUTES

Teleconference Meeting Minutes

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

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

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Teleconference

Meeting Chair:

External Lead: Sandra Arnold

Meeting Recorder:

FDA Attendees:

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

Project Manager, DRUDP (HFD-580)

External Participants:
Sandra Arnold, Population Council
The Danco Group
Nancy Buc, Buc and Beardsley

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

Discussion:
Distribution system:

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

- The proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient.

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

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

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

Phase 4 commitments

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

Action Items:

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

Minutes Preparer **Concurrence, Chair**

cc:
Original NDA
HFD-580/DivFile
HFD-580/ [redacted]
HFD-580/ [redacted]

Drafted: May 19, 2000/ [redacted]
Initialed [redacted]
Final: May 23, 2000

MEETING MINUTES

Meeting Minutes

Date: April 24, 2000 **Time:** 12:00 – 1:00 PM **Location:** Parklawn; 17B-43

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

Indication: induction of abortion

Sponsor: Population Council

Type of Meeting: Status Meeting

Meeting Chair:

Meeting Recorder:

FDA Attendees:

, Office of Drug Evaluation III (ODEIII; HFD-102)
, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
DRUDP (HFD-580)
, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Chemist, DNDCII @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (FD-580)
Regulatory Project Manager, DRUDP (HFD-580)
Project Management Staff, DRUDP (HFD-580)
Office of Post Drug Review Assessment (OPDRA; HFD-
OPDRA DDRE2 (Division 2) (HFD-440)
Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To evaluate the March 30, 2000 submission for completeness and update the team on the goal dates for this application.

Background: This NDA was originally submitted on March 14, 1996 receiving an approvable action on September 18, 1996. This application had a complete response dated August 18, 1999 and received another approvable action on February 18, 2000. This resubmission dated March 30, 2000 was submitted as a complete response by the sponsor.

Decisions made:
Chemistry

Biopharmaceutics

- the sponsor has included the metabolism information in the label, as requested by the reviewer and has accepted the dissolution specification

Action Items:

- send acknowledgement letter of complete response as a Class 2 resubmission to the sponsor (completed)
- will be working with on the Black Box Warning and Distribution System
- provide with the foreign label that the sponsor provided in this submission (completed)
- send consult to the thalidamide working group (completed)
- to provide with copies of FDA letters sent out regarding restricted distribution programs

Minutes Preparer **Concurrence, Chair**

Meeting Minutes

Date: May 16, 2000 **Time:** 3:00-4:00 PM **Location:** Parklawn; 17B-43

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

Indication: Medical termination of pregnancy

Sponsor: Population Council

Type of Meeting: Status Meeting

Meeting Chair:

Meeting Recorder:

FDA Attendees:

)ffice of Drug Evaluation III (ODEIII, HFD-103)
.r, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)

, @ DRUDP (HFD-580)

@ DRUDP (HFD-580)
Office of Post Drug Review Assessment (OPDRA, DDRE2, HFD 440)
, OPDRA (HFD-440)
Project Management Staff, DRUDP (HFD-580)
Project Manager, DRUDP (HFD-580)

Meeting Objective: To continue discussions regarding the March 30, 2000 resubmission.

Background: This NDA was originally submitted on March 14, 1996 receiving an approvable action on September 18, 1996. This application had a complete response dated August 18, 1999 and received another approvable action on February 18, 2000. The sponsor submitted this resubmission dated March 30, 2000 as a complete response.

Discussion:
Chemistry

- the facilities inspection has been requested, but there is no date entered in the system; the chemist will speak to the inspector before the inspection takes place for final advisement
- the sponsor will be submitting more data for review

Clinical:

- **approval under Subpart H:** meeting to be scheduled with [redacted] to discuss if this NDA meets Subpart H requirements (serious and life threatening condition)
- **discussion regarding provider qualifications:**
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- **Phase 4 studies:** sponsor will be requested to submit summary protocols for review for Phase 4 protocols, as part of the approvability requirements for this NDA
- **Distribution System** [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- **Other Issues:**
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Action Items:

- [redacted] the sponsor to discuss provider qualifications and the need for Phase 4 protocols to be submitted during this review cycle

- [redacted] for further discussion of clinical issues
- [redacted] to schedule meeting regarding Subpart H requirements with [redacted]

/S/

Minutes Preparer

/S/

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/
HFD-580/
HFD-580/
HFD-102
HFD-440/

Drafted: May 17, 2000/N20687mtg051600.doc
Initialed:
Final:

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	June 23, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza, New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

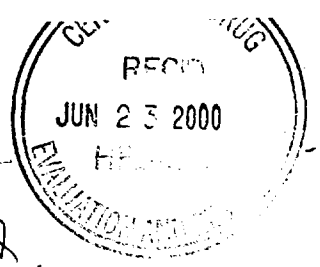
NUMBER OF VOLUMES SUBMITTED: 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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

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

MIF 007820

Danco Laboratories, LLC



June 22, 2000

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

Reviewed 9/27/00

ORIG AMENDMENT

BC

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

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

Dear

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

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

A. Validated Process Adjustments

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

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

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

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

B. Other Corrections

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

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

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

Sincerely,

President and Chief Executive Officer

REVIEWS COMPLETED
CDD ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO
CDD INITIALS DATE

Enclosures
cc: Sandra P. Arnold – Population Council
Nancy L. Buc, Esq. – Buc & Beardsley
Danco Laboratories, LLC
Frederick H. Schmidt – Population Council

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	June 22, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* One Dag Hammarskjold Plaza New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

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

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

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

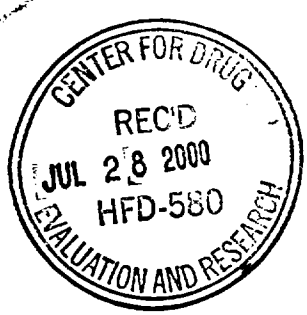
MIF 007823

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

noted 7/29/00

ORIGINAL



July 27, 2000

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

ORIG AMENDMENT

BC

REVIEWS COMPLETED
CSO ACTION
LETTER N.A.I. MEMO
CSO INITIAL DATE

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 054: Further response regarding labeling and distribution;
Follow up to July 19, 2000 Meeting

Dear

We thought our July 19, 2000 meeting was very informative and helpful, and we appreciate your responsiveness and that of your colleagues. In this letter, we address the issues raised or left open at the July 19 meeting.

For the most part, we have used the same numbering system as we did in our July 5 letter. We have not used the captions from that letter, because many of the issues they raise have already been resolved; instead, we use new captions which capture the nature of the issue. The last issue discussed in this letter was not discussed in the July 5 letter and therefore has no number.

1. Black box warning

[ ]

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

2 and 8. Physician Training

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

10. Incidence of Need for Curettage

13. **Timing of Dose of Misoprostol**

17. **Carcinogenesis, Mutagenesis, Impairment of Fertility**

26. **Provider Qualifications**

34. PATIENT AGREEMENT

Encouraging and Documenting Provision of Information to Patients

* * *

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 27, 2000
TELEPHONE NO. (Include Area Code)	FACSIMILE (FAX) Number (Include Area Code)
(212) 339-0663	(212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
One Dag Hammarskjol Plaza New York, New York 10017	

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

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

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

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

MIF 007833

ATTACHMENT C: Articles Regarding Home Use

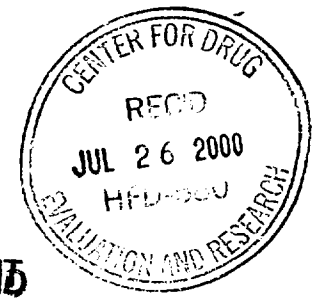
ATTACHMENT D: Articles Regarding Onset of Puberty

Danco Laboratories, LLC

July 25, 2000

ORIGINAL

Received 11 CT 00



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

DRUG AMENDMENT

BC

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
Amendment 053 - Additional Stability Data on Drug Product
- Revised Stability Commitment
- Mock-Up Sample of the Primary Package and its Blister Card

Dear

Pursuant to our telephone conversation with on July 20, 2000, we are providing the agency with the following information:

A. Additional Stability Data on Drug Product

Twelve (12) and nine (9) month long term stability data on Danco's Drug Product Lots #99005 and #99007, respectively, are enclosed (see Attachment A). Six (6) month accelerated data on these same two production-scale lots were previously supplied in Amendment 040 dated January 28, 2000 (Lot #99005) and Amendment 044 dated April 20, 2000 (Lot #99007).

These new data continue to show excellent long-term stability performance for Danco Drug Product. These results, as well as the previously provided stability data on Roussel Drug Product, demonstrate that the initial expiration dating period should be established at months.

B. Revised Stability Commitment

We have revised the Stability Commitment (see Attachment B) to clearly indicate that a Prior Approval Supplement will be filed with FDA if Danco wishes to use pre-approval batch data to request extension of the initial expiration dating period.

In addition, we have corrected the typographical error in the cover page to Attachment C of Amendment 047, dated May 17,2000, to read "Drug Product" rather than "Drug Substance" (see Attachment C)

C. Mock-Up Sample of the Primary Package and its Blister Card (See Enclosure)

Each blister card has a designated "print area" where the following information will be printed: (1) the Lot/ID number (11 digits), (2) the expiration date and (3) the "data matrix square" represented by "▣". The unique Lot/ID number is composed of

All of this information also is reflected in the code printed in the data matrix square. The code in the data matrix square is readable by a hand held scanner and permits the tracking of each individual blister card. This designated "print area" of the blister card is visible through a cutout window of the primary package, thus providing easy access and readability for batch information. This is more fully described in the previously submitted Distribution Plan.

Since the original production of the mock-up of the blister card and primary package, we have made the following changes which will appear on the final packaging:

- "MIFEPREX® (Mifepristone Tablets 200mg)" that appears on the package and the blister has been changed to "MIFEPREX® (Mifepristone) Tablets, 200mg".
- The following storage statement has been added to the blister card: " Store at 25°C (77°F)" .

We believe that the trademark is prominently placed on the primary package and that a location change would not improve its prominence.

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

Sincerely

President and Chief Executive Officer

/dns
Enclosure
cc: Sandra P. Arnold — Population Council

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ E-MAIL ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 25, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

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

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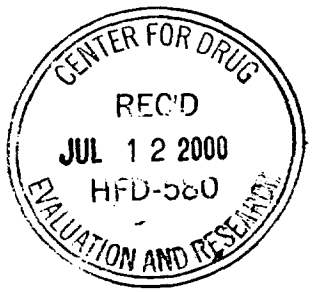
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

MIF 007847

Population Council

ORIGINAL



Sandra P. Arnold
Vice President
Corporate Affairs

July 11, 2000

BY HAND

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

NEW CORRESP
NC

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

Dear

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

Sincerely,

Sandra P. Arnold 7/13

Sandra P. Arnold

REVIEWS COMPLETED

CSO ACTION: ☐ LETTER ☒ MEMO

2/13/00

CSO INITIALS DATE

cc:
President and Chief Executive Officer
Danco Laboratories, LLC

MF 007848

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

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PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

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REASON FOR SUBMISSION

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Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

September 22, 2000

NEW CORRESP

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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 065; Revision to Prescriber's Agreement

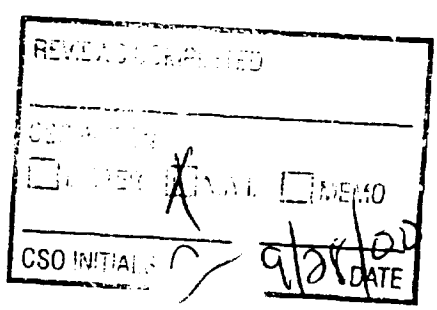
Dear

I am enclosing a revised Prescriber's Agreement/Order Form. The only difference from previous versions is the correction of telephone numbers.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold



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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

SEP 27 2000

September 22, 2000

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

9/21/00

ORDER FORM

To order MIFEPREX™ (Mifepristone) Tablets, 200 mg, just follow the 7 steps below.

1. Select quantities of Mifeprex* (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

_____ pkg./each 3 tablets Mifeprex
_____ box/12 pkgs. Mifeprex

2. Billing Information

Bill to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

3. Shipping information. Check if same as above.

Ship to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

4. Additional site locations

I will also be prescribing Mifeprex at these additional locations:

Name	**Address**	**City**	**State**	**Zip**	**Phone#**	**Fax#**

(Any additional sites may be listed on an attached sheet of paper.)

5. Request additional materials:

☐.Medication Guide
☐.Patient Agreement
☐.State Abortion Guidelines

6. Establishing Your Account (required only with first order)

Each facility purchasing Mifeprex is required to be included in your account information (see #4) before the distributor can ship the product. Read the Prescriber's Agreement on the reverse of this order form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name_____ Signature_____

Medical License # _____ Date_____

7. Fax this form to a distributor(s) of your choice below.

Distributor A
Address
Phone
Fax

Distributor B
Address
Phone
Fax

* Mifeprex is a trademark of Danco Laboratories, LLC

APPEARS THIS WAY
ON ORIGINAL

MIFEPREX™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Training in the administration of mifepristone is very important. A full range of training materials and opportunities with continuing medical education (CME) credit is readily available through Danco Laboratories' website, www.earlyoptionpill.com and our toll free number, 1-877-4 Early Option (1-877-432-7596). Please read the attached page, "Training Opportunities" to identify which program is most appropriate for you.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

9/__—/00

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Phone _____ Fax _____
Attention _____ Purchase Order #_____

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By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name_____ Signature_____

Medical License # _____ Date_____

7. Fax this form to a distributor(s) of your choice below.

Distributor A
Address
Phone
Fax

Distributor B
Address
Phone
Fax

* Mifeprex is a trademark of Danco Laboratories, LLC

APPEARS THIS WAY
ON ORIGINAL

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(Mifepristone) Tablets, 200 mg

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Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-4[illegible]-7596)
www.earlyoptionpill.com

Population Council

ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

September 27, 2000

ORIG AMENDMENT

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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 067; Revisions to Package Insert and
Prescriber's Agreement/Order Form

Dear

I am enclosing a revised package insert and a revised Prescriber's Agreement/Order Form. In accordance with telephone discussions today about training opportunities, we have deleted the penultimate paragraph (beginning "Please review . . .") under DOSAGE AND ADMINISTRATION in the package insert, the last paragraph of text (beginning "Training in .. .") in the Prescriber's Agreement, and the Training Opportunities sheet.

Sincerely,

Sandra P. Arnold /sb

Sandra P. Arnold

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

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

MIFEPREX™ (mifepristone) Tablets, 200 mg
For Oral Administration Only

If Mifeprex* 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 Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 191-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

* Mifeprex is a trademark of Danco Laboratories, LLC.

CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E_2. All other women without an apparent expulsion took a 400 µg dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

Table 1

Outcome Following
Treatment with Mifepristone and Misoprostol in the U.S. and French Trials

	U.S. Trials		French Trials	
	N	%	N	%
Complete medical abortion	**762**	**92.1**	**1605**	**95.5**
Timing of expulsion				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
– less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	**65**	**7.9**	**76**	**4.5**
Reason for surgery				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	**827**	**100**	**1681**	**100**

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 μg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

WARNINGS
(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35

years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the PATIENT AGREEMENT. (Additional copies of the Medication Guide and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see Medication Guide).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2

Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	Mifepristone-Misoprostol	Total
Subsequently had surgical abortion	**3**	**7**	**10**
No abnormalities detected	*2*	*7*	*9*
Abnormalities detected (sirenomelia, cleft palate)	*1*	*0*	*1*
Subsequently resulted in live birth	**13**	**13**	**26**
No abnormalities detected at birth	*13*	*13*	*26*
Abnormalities detected at birth	*0*	*0*	*0*
Other/Unknown	**26**	**20**	**46**
Total	**42**	**40**	**82**

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the U.S. and French trials are shown in Table 3.

Bleeding and cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3

Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence >1% are included.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the healthcare provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 μg tablets (400 μg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured for:
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

MEDICATION GUIDE

Mifeprex (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex and misoprostol. It will help you understand how the treatment works. This Medication Guide does not take the place of talking with your health care provider (provider).

What is the most important information I should know about Mifeprex?

Mifeprex is used to end an early pregnancy. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. By using Mifeprex, you probably will not need a surgical procedure to end your pregnancy.

When you use Mifeprex, you also need to take another medicine called misoprostol. You take misoprostol 2 days after you take Mifeprex.

You need to sign a statement (PATIENT AGREEMENT). Before you get Mifeprex, you will need to read and understand the information in this Medication Guide. Then you will need to sign a statement that you have decided to end your pregnancy.

You must visit your provider on Day 1, Day 3, and about Day 14. See the section called "How should I take Mifeprex?" for information about what happens at each visit. If you do not follow all the steps in "How should I take Mifeprex?" you will not know if your pregnancy has ended.

What to do if you are still pregnant after Mifeprex or Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Symptoms to expect. This treatment causes cramping and bleeding. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you **must return** to your provider on Day 3 and about Day 14.

If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol. This is a medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9-16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue that come from your uterus. This is an expected part of ending the pregnancy.

Heavy bleeding and the need for surgery. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (curettage) to stop it. This is why you must talk with your provider about what to do if you need emergency care to stop heavy and possibly dangerous bleeding.

Before you take Mifeprex. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider will also give you the name and phone number of who will handle emergencies.

Talk with your provider. You and your provider should discuss the benefits and risks for you of using Mifeprex.

What is Mifeprex?

Mifeprex blocks a hormone needed for your pregnancy to continue. When used together with another medicine called misoprostol, Mifeprex ends your pregnancy. About 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this Medication Guide.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - Your provider will check to see if you are still pregnant.
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your health care provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 2 weeks after you took Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

You should not take certain other medicines, because they may interfere with the treatment. Ask your provider about what medicines you can take for pain. Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop using your breast milk for a few days.

What are the possible side effects of using Mifeprex?

See the section "What is the most important information I should know about Mifeprex?" for symptoms to expect.

In some cases, bleeding can be very heavy. In a very few cases, this bleeding will need to be stopped by a surgical procedure. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding.

Other side effects of the treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

If you are worried about any side effects you have, talk with your provider about them. Your provider will give you a telephone number to call if you have any questions, concerns, or problems. Your provider's telephone number is _____.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This Medication Guide has been approved by the US Food and Drug Administration.

PATIENT AGREEMENT
Mifeprex (mifepristone) Tablets

1. I have read the attached Medication Guide for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office.
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have the provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:

- return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
- return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the Medication Guide for mifepristone.

Provider's Signature: _____

Name of Provider print: _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the Medication Guide to the patient.

9/21/00

ORDER FORM

To order MIFEPREX™ (Mifepristone) Tablets, 200 mg, just follow the 7 steps below.

1. Select quantities of Mifeprex* (Mifepristone) Tablets, 200 mg; NDC 64875-001-03
_____ pkg./each 3 tablets Mifeprex
_____ box/12 pkgs. Mifeprex

2. Billing Information
Bill to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

3. Shipping information. Check if same as above.
Ship to Name _____
Address _____
City _____ State _____ ZIP _____
Phone _____ Fax _____
Attention _____ Purchase Order #_____

4. Additional site locations
I will also be prescribing Mifeprex at these additional locations:

Name	**Address**	**City**	**State**	**Zip**	**Phone#**	**Fax#**

(Any additional sites may be listed on an attached sheet of paper.)

5. Request additional materials:
☐.Medication Guide
☐.Patient Agreement
☐.State Abortion Guidelines

6. Establishing Your Account (required only with first order)
Each facility purchasing Mifeprex is required to be included in your account information (see #4) before the distributor can ship the product. Read the Prescriber's Agreement on the reverse of this order form and sign below.
By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name_____ Signature_____

Medical License # _____ Date_____

7. Fax this form to a distributor(s) of your choice below.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

* Mifeprex is a trademark of Danco Laboratories, LLC

APPEARS THIS WAY
ON ORIGINAL

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

FACSIMILE TRANSMISSION

September 22, 2000

Please deliver to: t)

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

Total Pages (including cover sheet): 6

COMMENT:

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

BUC & BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE
202-736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

September 21, 2000

Division of Drug Marketing, Advertising and Communications (HFD-42)
Center for Drug Evaluation and Research
Room 17 B-20
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-687, Mifeprex (mifepristone) Oral Tablets
MACMIS #9342

Dear

In the rush last night, I included a draft page 2 instead of a corrected page 2 in my letter. I am attaching a complete copy of the letter, including the correct page 2.

Sincerely,

Nancy L. Buc

Danco Laboratories, LLC

August 24, 2000

ORIGINAL

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

AMENDMENT

Reviewed

9/27/00

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

- Amendment 056 - Drug Substance Chemistry, Manufacturing and Controls (CMC)
  -Discontinuance of
  Method

Dear

Given the development, validation and implementation since January 1999 of method for the Assay of Mifepristone, the original method will be discontinued as a release method for the drug substance, effective September 1, 2000. The manufacturer's Final Product Specifications for mifepristone drug substance have been revised to reflect that change (see enclosed).

Sincerely,

President and Chief Executive Officer

/dns
Enclosure

Cc: Sandra P. Arnold – Population Council

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	August 24, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*

DOSAGE FORM Tablet	STRENGTHS 200 mg	ROUTE OF ADMINISTRATION Oral

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

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

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

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

MIF 007886

Population Council ORIGINAL

Sandra P. Arnold
Vice President
Corporate Affairs

September 20, 2000

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

ORIG AMENDMENT

13 C

Re: NDA 20-687, Mifepristone 22 mg Oral Tablets
Amendment 063, Initial Promotional Labeling

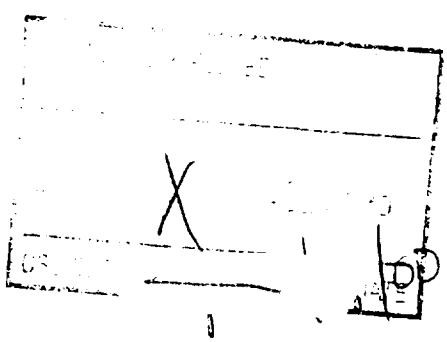
Dear

I am enclosing 10 copies of materials which we intend to use immediately upon approval. I would appreciate your arranging for DDMAC to review them as soon as possible, but no later than Friday, September 22. Please feel free to call Nancy Buc with any comments or suggestions.

Sincerely,

Sandra P. Arnold 9/20

Sandra P. Arnold



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

ORIGINAL

Danco Laboratories, LLC

September 15, 2000

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 061 - Initial Promotional Materials

Dear

I am enclosing 10 copies of our promotional materials that we wish to utilize around the NDA approval date. As agreed, could you please provide us with DDMAC's review comments as rapidly as possible, but no later than Wednesday, September 20. Please feel free to call me at any time if anything needs immediate clarification or discussion.

The materials enclosed are as follows:

- Formal announcement (press release)
- Fact sheet
- Fast Facts
- Video News Release (VNR) script
- Patient Brochure
- Tollfree Number script
- Website copy
- Provider Announcement (fax)

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

Additional materials that we need to use immediately following approval will be submitted for expedited review as soon as we have received your feedback on the first batch of materials.

Thank you for your assistance.

Sincerely,

President and Chief Executive Officer

/dns
Enclosures

Cc: Sandra P. Arnold – Population Council

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	September 15, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza, New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*

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

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

APPLICATION INFORMATION

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

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

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

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

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

MIF 007890

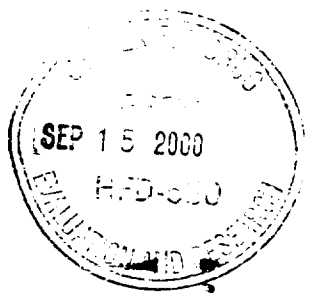
ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 15, 2000

BL
ORIG AMENDMENT



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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 060; Further response regarding
open issues

Dear

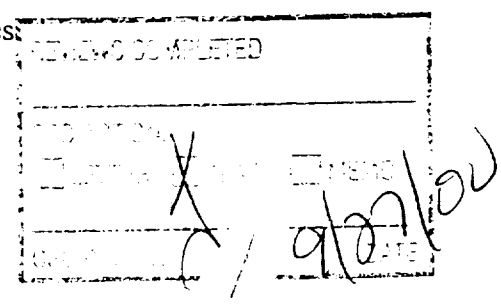
I am enclosing the prescribing information (package insert), Prescriber's Agreement, Order Form, Medication Guide, and Patient Agreement, as revised in accordance with discussions this week.

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

We commit to conduct post-approval the following studies:

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

II. A surveillance study on outcomes of ongoing pregnancies



Sincerely,

Sandra P. Arnold

Sandra P. Arnold

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

Dear :

We are pleased that you wish to become a provider of Mifeprex™ (mifepristone), which is indicated for early medical abortion up to 49 days from the first day of the patient's last menstrual period (see product label for full prescribing information). Product label, patient information and patient acknowledgment forms will be provided together with your order of Mifeprex™. Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below.

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to assure patient access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation, if necessary.

In addition to these qualifications, you must provide Mifeprex™ in a manner consistent with the following guidelines:

- You must fully explain the procedure to each patient and obtain each patient's signed acknowledgment. You should not give Mifeprex™ to any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen.
- Each package of Mifeprex™ has a unique identification number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record as well as on the corresponding patient acknowledgment form.
- While serious adverse events associated with the use of Mifeprex™ are rare, you must report any hospitalization, transfusion or other serious event to the distributor, identifying the patient solely by dose number to ensure patient confidentiality.
- The patient's follow-up visit is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify the distributor in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.

By signing below, you acknowledge receipt of this letter and agree that you meet these qualifications and that you will follow these guidelines for use.

_____ _____

Print Name Signature

BNDD#:_____ Medical License #:_____

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

FACSIMILE TRANSMISSION

9-20-00

Please deliver to:

From: Nancy L. Buc 202 736 3600 (f) 202 736 3610 (t)
Sender's Direct Dial

Total Pages (including cover sheet): 6

COMMENT:

/s/ 9/20/00

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

NANCY L. BUC
BUC & BEARDSLEY
202-736-3610

9/20/00

Dear ——

The 10 copies will be hand delivered in the morning but I wanted to get this to you today.

Nancy

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 20, 2000

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

Re: NDA 20-687, Mifepristone 22 mg Oral Tablets
Amendment 063, Initial Promotional Labeling

Dear

I am enclosing 10 copies of materials which we intend to use immediately upon approval. I would appreciate your arranging for DDMAC to review them as soon as possible, but no later than Friday, September 22. Please feel free to call Nancy Buc with any comments or suggestions.

Sincerely,

Sandra P. Arnold

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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 19, 2000

ORIG AMENDMENT

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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 062; Revised materials

Dear

I am enclosing new versions of the package insert, Medication Guide, and Patient Agreement. They have been revised in accordance with our discussions with you this week. I have also enclosed a new version of the Training Opportunities sheet, which has a phone number for NAF different from the one previously submitted. Also enclosed are the Phase IV protocol summaries.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

9/20/00

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

Phase IV Studies of Mifepristone

Study I

Study of Patient Outcomes From Referring and Non-referring Physicians

I. Introduction

Although medical abortion using a combination of mifepristone and misoprostol is very safe with few serious adverse events requiring emergency treatments, some women may require medical care during the procedure. Approximately 1% of women may require a medically necessary surgical intervention for bleeding, pain or discomfort before their follow-up visits. In addition, up to 1% of women in previous clinical trials have received IV-fluids and some women required in-patient hospitalization. Many providers of mifepristone-misoprostol medical abortion will also perform any medically necessary surgical interventions. However, some providers of medical abortion may refer their patients requiring surgical interventions to other health care providers. This study will investigate the safety of providing medical abortion services among these two types of providers.

II. Objectives

A. **Primary Study Objective** – Study patient safety outcomes based on their physician's possession of surgical intervention skills.

B. **Secondary Study Objectives:**

1. Study the impact of age and smoking status on safe and effective use of mifepristone.
2. Study the provider's compliance with the labeling requirement that providers and women sign the Patient Agreement.
3. Study the patient's compliance with labeling to return for follow-up on Day 14.

III. Study Design, Materials, and Methods

A. Study Approach

This study will be a prospective cohort study of women treated with mifepristone-misoprostol to terminate their pregnancies. This is not an efficacy study but a study of actual use of mifepristone in medical practice.

B. Data Source and Sample Selection

1. State selection

Given the geographic variation in medical practice, it has been suggested that the study should cover the following four states: California, New York, Texas and Florida. In 1996, these four states accounted for 50% of surgical abortions in the United States. We may propose an adjustment to this recommendation if, in the first six months, our mifepristone distribution data

do not support the selection of these four states. However, the study will include at least one of these four states.

2. Provider selection

In our selected state(s), preliminary data on physician's surgical intervention skills will be obtained. Based on the current caseloads of the providers, a weighted probability sample of providers who currently perform surgical abortion and a weighted probability sample of providers who currently do not perform surgical abortion will be selected. For the purpose of sampling, those providers who perform an insignificant number of mifepristone abortions in the first-year of the distribution will be dropped from the master list (i.e. the list from which a sample will be selected). The number of providers needed will depend on: 1) the total sample size for each group (see sample size calculations below), and 2) the caseload of each provider. Stratification by the selected states is necessary before sampling.

3. Patient selection

Since most providers will not keep a log of patients who are going to have a mifepristone abortion, we will not be able to draw a probability sample of patients. Instead, we will enroll patients consecutively from each provider until the provider's quota is met.

C. Inclusion/Exclusion Criteria

We will enroll all women who are eligible for mifepristone-misoprostol medical abortion and who wish to participate in this study, regardless of age, gestational age or smoking status.

D. Data Collection Methods

The study will begin one year after the introduction of mifepristone in the United States market, and enrollment will last approximately 12 months. Prior to initiating the study, we will visit each participating clinic and train the designated staff person(s) on the objectives of the study. We will also review the protocol, informed consent forms, and study instruments. In addition to the patients' medical records, providers will fill out study forms specifically designed to collect information on safety variables such as in-patient hospitalizations, IV-fluid administration, medically necessary surgical interventions, blood transfusions, and deaths. In addition, these forms will record data on women's age, smoking status, compliance with returning for their follow-up visit. The forms will also document whether women and providers sign the Patient Agreement forms.

At the end of each month, the study forms will be submitted to the Population Council in New York for analysis. Periodic site visits will be made by the principal investigators to review patient files and clinic recording systems to assure the integrity of the data collection. Data entry, cleaning and analysis will be conducted by staff at the Population Council immediately following project completion and results will be summarized and submitted to the FDA.

E. Outcome Variables

The primary objective is to study safe use of mifepristone. The outcome safety variable will be the percentage of cases that have one or more of the following events: hospitalization, medically necessary surgical intervention, and IV–fluid administration (which will be analyzed as a combined rate, not as separate rates of each adverse event). We will also record data on other variables, such as death, blood transfusion, failure to return for the follow-up visit at Day 14, and failure to obtain a PATIENT AGREEMENT before the treatment, which are all patient-level variables.

F. Main Independent Variable and Other Co-variants

The main independent variable is whether the medical abortion provider currently provides surgical interventions. Other provider-level variables include provider specialty (ObGyn vs. Family Practice Physician), practice site (urban vs. rural), and type of practice (solo vs. group). Two patient-level variables which will also be collected in the study are smoking status and age of patient. Additional provider-level variables, which may be related to future risk management programs, will be included if one group of providers has significantly higher rates of hospitalization, medically necessary surgical interventions, and IV-fluid administration.

G. Analytical Plan and Sample Size Calculation

Based on the objective of the study, we will use the rate of hospitalization, medically necessary surgical intervention, and IV-fluid administration (combined rate) to calculate the sample size. Based on the US clinical trials, we assume that 2% of women in the non-referrer group will need such interventions. We would like to demonstrate that no more than 7% of women in the referrer group would need such interventions. Using a two-tailed test and based on a power of 0.80 and an alpha of 0.05, we would need a final sample of 308 women in each arm for a total 616 women. These sample size calculations use a continuity correction. If we allow for a loss to follow-up rate of 15%, we would need to enroll 355 women in each arm for a total of 710 women.

H. Strengths, Limitations and Biases

One of the main advantages of this study is that it will provide a realistic assessment of the safety of providing mifepristone-misoprostol medical abortions in actual medical practice. Specifically, it will document providers' ability to facilitate referrals when necessary and women's ability to access care via this referral system. It will also investigate any potential effect of smoking status and age on the safe use of mifepristone medical abortion. It will also ensure that providers are fulfilling the requirement of obtaining a signed Patient Agreement. Lastly, it will provide some insights and additional information about the outcome of abortions among women who do not return for their follow-up visits.

There are three main limitations to this study. First, given this sample size, we will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths. Second, in some cases it may be difficult to

follow a woman who has been referred to another provider for a medically necessary surgical intervention. Every effort will be made to track and record the outcome in such cases. Nonetheless, if we are unable to verify the outcome of these women, they will be counted as failures since their primary providers clearly decided they needed a surgical intervention. Finally, we anticipate some difficulties in locating women who do not return for their follow-up visit. Upon enrollment in the study all women will be asked permission to contact them at home should they fail to return for their last visit. Using this contact information, we will attempt to determine whether they had a hospitalization, medically necessary intervention, and/or received IV-fluids.

There are several potential biases relating to the type of provider which may affect the rate of surgical interventions prior to the follow-up visit in these two cohorts. Since non-referrers will have the skills and equipment nearby, we hypothesize that they will be more likely than referrers to intervene unnecessarily and, thus, artificially increase the medically necessary intervention rate. Conversely, some referrers may be more likely to intervene (or give the woman a referral for an intervention) because they will have, on average, less experience and will be less comfortable waiting for the completion of the abortion process.

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