Conclusion

The anti-abortion movement has forced doctors into bullet-proof vests, subjected patients to screaming, abusive crowds, gotten politicians involved in private health care decisions, and now threatens to distort an important decision by the FDA from one based on science to one which appears to be influenced by political pressure. It would be a historic tragedy, a threat to the fundamental principles governing the practice of medicine, to allow this to happen.

RU-486 is safe and effective, as the FDA itself said in 1996. RU-486 will bring privacy back to a procedure that deserves it most. It will increase the number of providers offering abortion services. It will improve the availability of the earliest abortions, which are safest. And it will return abortion care to a private discussion and decision in the office of a doctor or other provider. As Donna Lieberman of the NYCLU pointed out: "The fundamental right to choose is a reality only when there is access to safe and effective methods of abortion."

Submitted ~~on~~ September 22, 2000, by

Mark Green, Public Advocate for New York City

Jo Ivey Boufford, M.D., Dean of the Robert F. Wagner School of Public Service

Allan Rosenfield, M.D., Dean of the Mailman School of Public Health

Victor W. Sidel, M.D., President of the Public Health Association of New York City

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 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

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

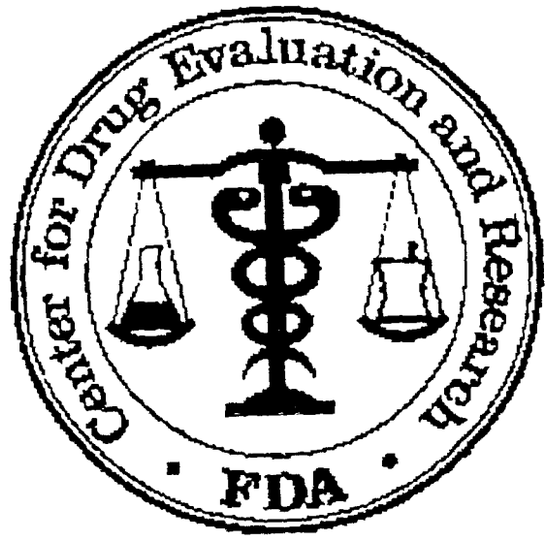
Sandra P. Arnold

APPEARS THIS WAY
ON ORIGINAL

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

FOOD AND DRUG ADMINISTRATION
DIVISION OF GICDP
DOCUMENT CONTROL, ROOM 6B-24
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: September 22, 2000



TO:

Name: ———

Fax No: ———

Phone No: ———

Location:

FROM:

Name: ———

Fax No: ———

Phone No: ———

Location: ——— /HFD-180

This fax is 29 pages long, which includes a 1 page cover sheet and a 28 page fax from Searle, which contains copies of the UK, French, and German labeling for Cytotec. Note the last sentence of the CONTRAINDICATIONS section (which is on page 20 of their fax).

/S/

APPEARS THIS WAY
ON ORIGINAL

United States Senate

WASHINGTON, DC 20510

September 21, 2000

Donna E. Shalala
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Madam Secretary:

We are writing in strong opposition to the possible Food and Drug Administration (FDA) approval of the abortion-inducing drug, RU-486,also known as mifepristone.

First, we object in principle to the approval of this drug because it s primary purpose is to induce an abortion.

As well, we are deeply concerned over recent reports regarding the manufacture of this drug and would therefore urge a more thorough and careful review before any approval is granted.

Particularly disturbing is a recent article, "Abortion-Pill Venture Keeps to Shadows Awaiting Approval" by Rachel Zimmerman *(Wall Street Journal, September 5, 2000, page A1)*. This article implies that Danco Industries has an arrangement with a business in China to produce the pills that, pending FDA approval, would be sold in the United States.

If correct, this information raises serious concerns that ought to be answered before any final decision is made to allow the importation of the abortion pill into the United States from China. We, therefore,strongly urge you to delay any further action on the approval of this abortion-inducing drug.

Respectfully,

Michael B. Enzi

Mike DeWine

T. Hutchinson

Bob Smith

Frank H. Murkowski

John Ashcroft

Jeff Sessions

APPEARS THIS WAY
ON ORIGINAL

New PI as of 9/22/00
– includes changes DDMAC wanted (+FDA)

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 21, 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 200 mg Oral Tablets;
Amendment 064; Revised labeling

Dear ———

I am enclosing a package insert (including Medication Guide and Patient Agreement) and a Training Opportunities sheet revised in accordance with discussions with you today.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

APPEARS THIS WAY
ON ORIGINAL

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

———————

———

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 /s/

Sandra P. Arnold

APPEARS THIS WAY
ON ORIGINAL

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

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

From:	**Jesse Helms**	*OS#:*	**092120000120**
Organization:	**Senator - North Carolina**	*Date on Letter:*	**9/18/00**
City/State:	**Washington DC**	*Date Received:*	**9/21/00**
On Behalf Of:		*Type:*	**Congressional**

Subject: **Abortion Drug, RU-486. Concerns re September 5, 2000, Wall Street Journal article, 'Abortion Pill Venture Keeps the Shadows Awaiting Approval,' which was based, in part, on leaked internal documents from Danco Laboratories. Also concerned about Danco deal with Communist China.**

Assigned to:	**FDA**	*Dep.ES:*	**Vacant**
PC:		*Date Assigned:*	**9/22/00**
Action Required:	**Sec Sig**	*Date Reassigned:*	
		Reply Due Date:	**10/6/00**

Info Copies To: **ASL; ASMB; ASPA; ASPE; DEP; ESS; NIH; OGC; OIA; OPHS; SAMHSA; SEC**

Interim (Y/N): **No** *Date Interim Sent:*

Comments:

File Index: **PO-4-5** *CCC:* ———

APPEARS THIS WAY
ON ORIGINAL

MO-5910

United States Senate
COMMITTEE ON FOREIGN RELATIONS
WASHINGTON, DC 20510–6225

September 18, 2000

The Honorable Donna E. Shalala
U.S. Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Madam Secretary:

I don't know whether you saw the September 5 Wall Street Journal article ("Abortion-Pill Venture Keeps the Shadows Awaiting Approval") which was based, in part, on leaked internal documents from Danco Laboratories.

Danco Laboratories, by the way, has pending before the FDA a letter seeking approval to market the RU-486 abortion pill in the United States.

I understand that Danco made a deal with Communist China for the manufacture of the abortion pills to be sold in the United States, *if FDA approval is granted*. If this is correct it raises a number of troubling questions:

(1) Is the facility in China a state-owned facility?

(2) Does the facility operate in accord with internationally recognized standards regarding worker safety, or with coercive or slave labor?

(3) Does the management of the facility enforce the birth-quota system, which involves the monitoring of all female employees' menstrual cycles for unauthorized pregnancies – and if so, what threats or penalties are applied to a female employee of the facility who becomes pregnant without a permit? (For example, is she threatened with the loss of her position unless she submits to an abortion?)

(4) Are abortion-inducing drugs already produced by the factory utilized as

part of the nationwide birth-quota enforcement system, which has been well documented to rely heavily on many forms of coercion?

(5) Does the facility produce the anti-coagulation drugs that are reportedly given to some condemned prisoners prior to their execution, in order to facilitate immediate harvesting of their organs, which are sometimes provided to Party officials or to foreign buyers?

(6) Does the facility produce any drugs used in the interrogation of political prisoners?

I hope and pray that approval of RU-486 is not forthcoming. Surely, your Department will have to address these and other questions to be raised by many others if the Administration should make the mistake of approving the marketing of a Communist Chinese-manufactured abortion pill in the United States.

Sincerely,

JESSE HELMS:ggg

Jesse Helms

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

TO	
DATE	TIME

PHONE CALLS
"WHILE OUT" RECORD

M. [redacted]

OF

PHONE [redacted]
AREA CODE NUMBER EXTENSION

TELEPHONED		PLEASE CALL	
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

MESSAGE
Has [redacted]
needs to review
RU 486
before 5

TAKEN BY:

APPEARS THIS WAY
ON ORIGINAL

MIF 001319

BEST POSSIBLE COPY

APPEARS THIS WAY
ON ORIGINAL

TELEPHONED		PLEASE CALL	
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

TO

DATE TIME

PHONE CALLS
"WHILE OUT" RECORD

M.

OF

PHONE
AREA CODE NUMBER EXTENSION

MESSAGE RU486

need info you expect receive being after yesterdays mtg

TAKEN BY:

TELEPHONED	✓	PLEASE CALL	✓
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

TO

DATE 9/18 TIME 3^00

PHONE CALLS
"WHILE OUT" RECORD

M. Nancy Bue

OF

PHONE 202 - 736 - 3610
AREA CODE NUMBER EXTENSION

MESSAGE mifepristone

TAKEN BY:

MIF 001320

PHONE 1-3[illegible]
AREA CODE NUMBER EXTENSION

TO _____

DATE 9/1 TIME [illegible]

PHONE CALLS
"WHILE OUT" RECORD

M. Nancy Sue

OF [illegible]

PHONE 202-736-3600 Sue's
AREA CODE NUMBER EXTENSION

TELEPHONED		PLEASE CALL	
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

MESSAGE Wall St. Journal will print article on Jackrustow Tues. Sept 5th

They were unable to stop it.

TAKEN BY: [illegible]

MIF 001321

AREA CODE NUMBER EXTENSION | TAKEN BY: _____

TO _____

DATE _____ TIME _____

PHONE CALLS
"WHILE OUT" RECORD

M _____ Jon Kilkenny

OF _____

PHONE _____
AREA CODE NUMBER EXTENSION

TELEPHONED		PLEASE CALL	
CALLED TO SEE YOU		RETURNED CALL	
WILL CALL AGAIN		URGENT	

MESSAGE _____

Aug 31, 4-5

RU 486

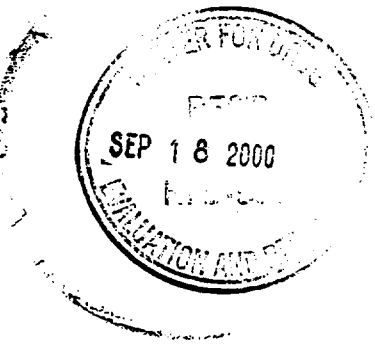
TAKEN BY: _____

ORIGINAL

Danco Laboratories, LLC

September 15, 2000

NEW CORRESP



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

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	September 15, 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)*: 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 001325

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 15, 2000

[redacted]

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

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

Dear [redacted]

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.

Subpart H

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

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

NDA 20-687

INFORMATION REQUEST LETTER

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

SEP 14 2000

Dear Ms. Arnold:

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

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

We are reviewing your revised Medication Guide and Patient Agreement for this application. We are providing you with our responses in the draft Medication Guide and the latest draft Patient Agreement in the attachments below.

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

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

Sincerely,

/S/ 9/14/00

———
—— Project Management Staff
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments: Medication Guide and Patient Agreement

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

~~NDA 20-687~~

Food and Drug Administration
Rockville MD 20857

INFORMATION REQUEST LETTER

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

SEP 13 2000

Dear Ms. Arnold:

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

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

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

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

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

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

Sincerely,

/S/

_____

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

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

Danco Laboratories, LLC

Reviewed /S/ 9/27/00

September 12, 2000 ORIGINAL

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

ORIG AMENDMENT

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

Dear ———

Per your request, I am enclosing underlying analysis to support the conclusion in the article by Spitz et al that outcomes in the clinical trials were unrelated to age.

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 ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

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

MIF 001329

Danco Laboratories, LLC

September 8, 2000

DUPLICATE

———

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

SEP 11 2000

ORIG AMENDMENT

BC

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

- Amendment 059 - Submission of Revised Mifepristone Substance Working Standard Specifications

Dear ———

Following our conversations with ——— today, we have included ——————— as an added specification for the mifepristone working standard.

Enclosed please find the revised Mifepristone Working Standard Specifications.

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

Sincerely,

President and Chief Executive Officer

APPEARS THIS WAY
ON ORIGINAL

/dns
Enclosure

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, Parts 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 6, 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 Hammarskjold 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	Mifeprex™

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)

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 OF 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 001331

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* Phase IV protocols, Subpart H, distribution plan

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sandra P. Arnold	Sandra P. Arnold, Vice President	09/06/2000
ADDRESS *(Street, City, State, and ZIP Code)* One Dag Hammarskjold Plaza, New York, NY 10017		Telephone Number (212) 339-0663

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 6, 2000

[redacted]

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

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 058; Further response regarding labeling
and distribution and other open issues;
Followup to August 4 meeting and August 9, 11, and 25
Telephone Calls

Dear [redacted]

As we said at our August 4 meeting with you and your colleagues, we continue to appreciate the "interactiveness" of the review process for mifepristone. It is evident that our submissions are receiving prompt and thorough attention, and we think the process is going well even as we engage with you on the relatively few remaining issues. This letter presents our views on these issues.

Subpart H

Although FDA continues to assert that mifepristone can be and will be regulated pursuant to 21 C.F.R. Subpart H, it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider.

By its terms, Subpart H applies only to drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses . . ." 21 C.F.R. § 314.500. Neither pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore

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

inapplicable for that reason alone. Neither is pregnancy nor unwanted pregnancy a "serious" or "life-threatening" situation as that term is used in Subpart H.

In the preamble to the final rule, FDA said that "seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one." 57 Fed. Reg. 58942, 58945 (1992). The plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy. Unlike, for example, cancer, HIV infection, disseminated mycobacterial infections, pulmonary tuberculosis, and treatment of breakthrough pain in cancer patients who are opioid-tolerant, which FDA has previously said were serious or life-threatening,[1] pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H. And although a pregnancy "progresses," that is hardly the same thing as the worsening of a disease that physicians call progression. Nor can FDA expand the ambit of Subpart H to reach pregnancy and unwanted pregnancy by purporting to exercise "judgment." Under the regulation, "judgment" is supposed to be a matter of whether a particular disease actually is serious, not a means of stretching the meaning of serious to cover entirely new categories of non-serious situations.[2]

We understand that FDA believes that it must treat pregnancy and unwanted pregnancy

---

1. CDER, NDAs Approved under Acclerated Approval (Subpart H), at http://www.fda.gov/cder/rdmt/accapp.htm, printed Aug. 31, 2000.

2. Denominating pregnancy or unwanted pregnancy as a serious disease may also trigger Section 113 of FDAMA, which requires notification to NIH of clinical trials of drugs intended to treat "serious and life-threatening diseases." The possibility that FDA's calling these conditions "serious" may result in consequences such as application of Section 113 of FDAMA should itself give the agency pause.

as "serious conditions" because it has previously done so in the context of the Benten litigation. Benten v. Kessler, 505 U.S. 1084 (1992); Benten v. Kessler, 799 F.Supp. 281 (E.D. N.Y. 1992); Benten v. Kessler, 1992 U.S. Dist. LEXIS 14747 (Sept. 30, 1992). That "position" seems to have been necessitated by the litigation and events surrounding it, so the context was quite different from the NDA context, but in any event, we remind the agency that unless a position is taken at the conclusion of an adjudication or notice and comment rulemaking, it is not entitled to Chevron deference, Christensen v. Harris County, 120 S.Ct. 1655, 1662 (2000).

Also, FDA is free to change its position if the situation warrants it, so long as it provides a "reasoned analysis" for why it has done so. Motor Vehicle Mfrs. Ass'n of the United States v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29 (1983). In Benten, FDA was defending an import alert which cast mifepristone as the unapproved new drug which it then was. FDA had not even received an NDA, much less reviewed one. Thus, the situation, if not the disease, was understandably a source of serious concern. Now, after safe and effective use in over 500,000 women, and following thorough FDA review for an NDA, mifepristone stands on the brink of approval, and the reason for the agency's concern in Benten will then be removed. An explanation resting on safe and effective widespread use and the submission, review, and approval of an NDA would easily satisfy the "reasoned analysis" standard.

FDA's insistence on Subpart H is particularly puzzling because it is so unnecessary. FDA explained ~~in its~~ preamble to the final Subpart H regulations that Section 505 of the Food, Drug, and Cosmetic Act permits approval of new drugs only if they are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. Also, if the labeling contains incorrect information about or fails to disclose details of conditions of use (including the distribution system), the drug may be misbranded. Finally, the approved

labeling, including the sections such as Dosage and Administration and How Supplied which (in mifepristone's case) reflect the approved distribution system, cannot be modified without FDA's prior approval, 21 C.F.R. § 314.70. 57 Fed. Reg. 58942, 58951 (1992).

As you know, the Population Council and Danco Laboratories LLC have proposed and committed to a distribution system acceptable to FDA, and have incorporated those commitments in the NDA in the form of labeling and Phase IV commitments. In light of the law as FDA has explained it in the preamble, the Population Council and Danco will be bound not only by their freely given commitment but also by law to carry out the distribution of mifepristone in accordance with the system presented in the NDA and approved by FDA, unless FDA approves an NDA supplement to change the system. The Population Council and Danco will also be bound by law not to change the distribution system without changing the labeling, and they cannot lawfully change the labeling without an approved NDA supplement. Thus, the NDA approval process wraps us up every bit as tightly as Subpart H.[3] Even if we were disposed to breach our commitments - which we are not - FDA would have available a wide range of remedies under the Food, Drug, and Cosmetic Act.

Invocation of Subpart H is also undesirable because it puts FDA in the position of making certain issues in this NDA more important than they actually are. As noted above, FDA has ample authority to demand compliance with the agreed-on distribution system and the approved labeling without invoking the Subpart H regulatory provisions that signal "big deal" to the pharmaceutical community. FDA has repeatedly and correctly stated that it will review

---

3. Please be advised that if FDA determines not to invoke Subpart H, and assuming DDMAC will provide the same immediate turn around promised for Subpart H materials, we will submit launch promotional materials, including the materials announcing NDA approval, for DDMAC review prior to their use.

mifepristone solely on the basis of science and the applicable statutory and regulatory law, and it does not need to and should not make any bigger deal of it than that.

Home Use

We continue to believe that the mifepristone/misoprostol regimen is safe and effective whether women take their misoprostol in the clinic or at home or another location of their choice. We recognize, however, that you have not yet made a decision on this point. In the meantime, for purposes of this letter, we have used the principles in the draft Medication Guide to incorporate the Day 3 Visit procedure in the draft labeling and other materials.

Phase IV

As we discussed at our August 4 meeting, the Population Council first proposed post-marketing studies more than four years ago, at an early stage of the review process. At that time, fewer data were available from both the United States and Europe than are now available, and the issues of concern were somewhat different than they are now that the agency has completed a much more thorough and focused review of the entire application. As new data have become available, some of the studies originally proposed have become unnecessary. Other studies, on reflection, seem unlikely to gather useful data at any reasonable cost or, in some cases, at any cost. On the other hand, issues that have arisen in the recent review process seem suited to further assessment by studies that the Population Council and Danco have agreed to undertake but which were not previously proposed. We discuss below the studies which we now believe should constitute our Phase IV commitments and those which we believe should be dropped.

The Study of Referrer and Non-Referrer Providers

As proposed by ——— this study, a protocol for which is attached, has as its

primary endpoint the failure rate of the mifepristone/misoprostol regimen. We will enroll 150 women in each arm of the study, which after losses to follow up should yield approximately 120 patients per arm, a number which should provide sufficient power to assess whether the patients in each arm have a failure rate more than 5 percentage points greater than the failure rate of 8% in the clinical trials. (The study is not a comparison of the failure rates in the two arms, but, rather, will provide information about whether both the referrers' and the non-referrers' patients do about as well as the patients in the clinical trial.) In addition, the study is designed to collect information on serious adverse events such as transfusion, hospitalization, etc. Because the occurrence of such events is quite low (typically less or much less than 1%), the study is not large enough to allow the kinds of comparisons to clinical trial results which should be possible with respect to failure rates, but it should be helpful in ruling in or out the possibility that serious adverse events are occurring much more frequently in the post-approval environment than in the clinical trials. We will also try to contact women who do not return for their Day 14 visit. See below, page 8, for a further discussion of this aspect of the study. We are committed to carrying out this study.

The Prescriber Audit

Under the distribution system proposed by the sponsor and discussed in the labeling, physicians who wish to order mifepristone will be required to signal their agreement to carry out certain obligations by signing the Prescriber's Agreement before the distributor may ship the drug to them. Among the important obligations physicians must undertake is obtaining signatures on the PATIENT AGREEMENT. The Prescriber Audit (protocol attached) will contact 200 randomly selected prescribers to ascertain whether they have obtained signed copies of the PATIENT AGREEMENT. We are committed to carrying out this study.

Studying On-Going Pregnancies for Information about Fetal Malformations

Some information on this subject is already available from Exelgyn's safety updates #9 and #10 (copies attached) and Table 2 in the draft package insert. Some additional information on the subject will also be available over time as physicians report on-going pregnancies to Danco, as provided in the Prescriber's Agreement and the prescribing information. With the help of prescribers and patients (if they consent), we intend to inquire further into these reports, as discussed in the Protocol, attached. We are committed to carrying out this study.

The Repeat Users Study

We have never been clear on why such a study would be useful. Nothing about the pharmacology of mifepristone suggests any carryover effect from one medical abortion to another, nor is there any reason to think that any aspect of the care of women who choose to have more than one medical abortion with mifepristone would be any different, even assuming, which we do not, that the provider was aware of their previous use of mifepristone. Thus, we would not expect the safety and efficacy of the drug to be any different in women who choose to use mifepristone a second time or more from the safety and efficacy in women using it for the first time. We do know that such a study will be very difficult and expensive to conduct. A woman who has once used mifepristone to terminate a pregnancy may, if she has another unwanted pregnancy, go to the same or a different provider, but unless both providers have agreed to participate in the study, there will be no way to catch the repeat use. Also, although providers may ask women considering medical abortion whether they have had previous medical or surgical abortions, they may not, and for reasons of privacy women may not volunteer this information. In short, it will be very hard to find women who are repeat users,

and not likely to be productive if we could. Therefore, we ask to be relieved of the obligation to conduct this study.

Lost to Followup Study

As part of the Study of Referrer and Non-Referrer Providers, we will obtain women's agreement to try to contact them if they do not return for their Day 14 visits, and we will attempt to locate everyone who does not return to learn as much as we can about their reasons for not doing so and their outcomes. (In some cases, as we have discussed, we believe the failure to return to the original provider will be because the provider to whom the woman was referred provides the necessary further care.) We believe this aspect of the Referrer/Non-Referrer Provider Study should be sufficient to constitute satisfaction of our commitment to follow the lost-to-follow- up patients.

Patients Over 35 or Younger Than 18 And/or Who Smoke

As reported in Spitz et al. (a copy of which was provided with my July 5 letter to you), outcomes in the clinical trials were unrelated to age. (There were 109 women 35 years of age or older in the clinical trial who were 49 days or less LMP.) Although age under 18 was an exclusion criterion in the clinical, that was not for any biological reason but rather because of the greater complexity of obtaining appropriate consent from minors. In fact, we do not believe there is any biological reason to expect different results in women younger than than those in the trial. We therefore do not believe that a study of women younger than 18 or older than 35 would provide useful data, and ask to be relieved of our obligation to conduct such a study.

Although there is no particular reason to expect smokers to do any better or worse than non-smokers, the question of smoking is almost always important, and we therefore propose to

conduct a study of 150 smokers of any age to see whether their failure rates are more than 5 percentage points different from the failure rates in the United States clinical trials. A summary protocol for this study is attached. We are committed to carrying out this study.

Response to [redacted] letter concerning changes to the package insert in CLINICAL PHARMACOLOGY; Metabolism subsection and PRECAUTIONS; Drug Interactions

We agree to make the suggested changes in the CLINICAL PHARMACOLOGY section, and have included these changes in the attached package insert. The suggested changes in the PRECAUTIONS section, however, are somewhat ambiguous. Is the reference to ' [redacted] ' in the sentence beginning [redacted] . ." a reference to misoprostol or mifepristone? The two sentences preceding the quoted language are about misoprostol, but the reference in the quoted language to CYP 450 suggests that "this drug" is mifepristone. Assuming that that is the case, we do not disagree that the drugs referenced in that sentence may inhibit metabolism of mifepristone. However, based on the literature on mifepristone and the available clinical information, we do not think any such inhibition of the metabolism of mifepristone, if it occurs at all, is likely to be of clinical significance. In this regard, it is important to note that mifepristone is administered in a single dose, and will be indicated for acute therapeutic use only. Also, there is quite a large margin of safety with the 600 mg dose. Hence, any inhibition of the enzymatic degradation of mifepristone that possibly could be caused by the presence of the referenced drugs or food would not be expected to result in accumulation of mifepristone in the body at levels approaching toxicity.

With respect to the second proposed sentence, concerning inducers of mifepristone metabolism, we do not think any effect on efficacy is likely. Assuming that inducers of

CYP450 3A4 enzymatic activity may accelerate metabolism of mifepristone, it has been shown that metabolism of mifepristone by CYP450 3A4 produces metabolites that are active at the same target receptor as the parent drug at the hypothesized concentration. Heikinheimo (1997). In this same study, it was concluded that the combined pool of mifepristone and its metabolites, rather than mifepristone alone, seems to be responsible for the biological actions of the drug. Thus, even if the metabolism of mifepristone were increased by one of the referenced drugs, there should be no difference in the efficacy or safety of the drug. See, also, Heikenheimo and Kekkonen (1993) (Although mifepristone can exhibit dose dependent effects, when used to terminate pregnancy, the effect is dose independent).

To confirm our views, we have reviewed the safety updates from January 1, 1991 through May 31, 2000, and the available adverse event reports and have found no indications that drug or food interactions have caused any safety problems. During the 1991 -2000 period, there was only one report of a putative drug interaction, and that was thought by Roussel Uclaf not to be caused by a drug/drug interaction. (See attached report.) In the report, Roussel Uclaf also acknowledged the relationship of CYP 3A4 enzyme induction and inhibition, but concluded that post-marketing surveillance data on mifepristone has not provided clinical evidence of any drug or food interactions. Roussel Uclaf also noted in the report that mifepristone has a wide therapeutic range, a point we want to reemphasize.

For these reasons, we think the language you proposed should be qualified, as follows:

> Although there have been no reports of adverse reactions or loss of efficacy because of drug or food interactions with mifepristone, on the basis of this drug's metabolism by CYP 450 3A4, it is possible that ketoconozole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism, or that rifampin, dexamethasone and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism.

[redacted] also inquired about corresponding revisions to the PATIENT INFORMATION (now the Medication Guide). The draft Medication Guide we received on August 31 deals with these issues by advising the woman not to take any other medicines or drugs at any time during the treatment procedure without consulting with her health care provider, and specifically advises her that other medicines may interfere with the treatment procedure. We agree with this approach.

Finally, [redacted] asks for a change to the PATIENT AGREEMENT concerning the fact that the treatment procedure does not always work completely. We have already made these changes; please see the version attached to our July 27 letter to you.

Response to [redacted] August 30, 2000 letter on Exhibit E, Draft Medication Guide, and PATIENT AGREEMENT

Exhibit E (Order Form and Prescriber's Agreement)

On the order form, we suggest revising Item 5 to read "Medication Guide" rather than "Patient Information."

On the Prescriber's Agreement (we do not object to changing the name), we have the following comments:

1. In the fourth paragraph and in the first bullet under the fifth paragraph, we suggest referring to "Federal law," a term which includes statutes, regulations, and case law, rather than the narrower "Regulations."

2. In the third bullet under the fourth paragraph, the word "severe" should precede "bleeding." As the prescribing information and the Medication Guide say, some bleeding is to be expected, and there is no need for a surgical intervention unless the bleeding is severe.

3. In the fifth paragraph, we propose deletion of the second sentence ([redacted]

[redacted]."). Information about the first, second, and third visits are included in the package insert, the Medication Guide, and the Patient Agreement. There is no reason to excerpt this particular portion of the regimen here.

4. We have revised the second sentence of the second bullet to read:

> 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.

We have also deleted the phrase about [redacted] because the prescriber is unlikely to know this information. Also, because we have agreed as part of our Phase IV commitments to try to obtain this information whenever an on-going pregnancy is reported to Danco, it is unnecessary for the physician to try to do so.

5. Our revised Prescriber's Agreement, attached, omits the last two sentences of the last bullet, because none of our Phase IV or other commitments contemplate anyone's (much less the sponsor's) visiting prescribers' offices for the purpose stated. As discussed with you and your colleagues, and as reflected in the discussion under Phase IV above, we do intend to conduct a telephone audit to ascertain whether providers are obtaining signatures on and retaining the signed PATIENT AGREEMENT.

Medication Guide - Mifeprex

1. In "Mifeprex is used to end an early pregnancy," we have deleted [redacted] because the statement is incorrect. In the clinical trials, mifepristone was shown to be effective at up to 63 days LMP, though less effective than at up to 49 days LMP. We have agreed with you to emphasize the 49 day concept, but we do not want to misstate the

efficacy of the drug to accomplish that purpose.

2. Because D&Cs are not the only or even the most common method of surgical abortion and not the only or even the most common surgical intervention for treating such conditions as severe bleeding, we have replaced "D&C" wherever it appears with either "surgical abortion" or "surgical procedure" as appropriate.

3. In "You need to sign a statement," we have added the phrase "('PATIENT AGREEMENT')" after the word "statement." We recognize the simplicity of the word "statement," but we also think it desirable to help the patient and the physician recognize that the statement in question is the PATIENT AGREEMENT. We also suggest reversing the order of the second sentence in this section so that the woman's reading the Medication Guide precedes, as it should, both her decision to end the pregnancy and her signing the statement. It reads as follows:

> Before you get Mifeprex, you will need to read the information in this Medication Guide and then sign a statement that you have decided to end your pregnancy.

4. In "You must visit your provider on Day 1, Day 3, and —— Day 14," we have deleted the word —— in the last sentence. These visits have two different purposes, to see whether the pregnancy has ended and to see whether the woman is OK, but the phrasing in the draft conflates the two.

5. In "What to do if you are still pregnant after Mifeprex treatment," we have deleted the last sentence concerning —————— We believe FDA has taken to overemphasizing this point, especially in light of the fact that there is no evidence that Mifeprex causes such damage.

Standard Warning

6. In "Symptoms to expect," it says the treatment causes —— cramping . . ." We

have deleted the word ——— in the interest of clarity. Also, because both the Day 3 and Day 14 visits are for a number of reasons, not just to check on the pregnancy, we have deleted that phrase. Finally, in the second paragraph, we have deleted ——————— in the next to last sentence; we believe it is more important to focus on what the woman will see than on its source.

7. Under "Heavy bleeding and the need for surgery," we have combined the first two sentences in a way that removes the somewhat inflammatory word ——— The revised language reads:

> 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.

8. In "Before you take Mifeprex," the text focuses on the prescriber's giving the woman the name, address, and phone number of the emergency provider before she takes the drug. We think this is jumping the gun in a way that may lead the woman to call the emergency provider when she could and should be calling the original prescriber. To remedy this problem, we have replaced this text with a revised version of the last paragraph under "What are the possible side effects of using Mifeprex." It reads as follows:

> 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.

Under this protocol, the prescriber can decide to handle all questions and concerns himself or herself, right up to the point where he or she decides to make a referral, and can then make the referral to the provider that is appropriate for the problem, or can make the referral at the time he or she prescribes the drug. Different prescribers will make different choices, and a

particular prescriber may make different choices for different patients, but they all fit the text we propose.

9. Under "What is Mifeprex," the first sentence has been revised to read "Mifeprex blocks a hormone needed for your pregnancy to continue." This revision avoids the problem presented by FDA's language, which implies that the woman needs her pregnancy to continue.

10. Under "Who should not take Mifeprex," we have revised the first bullet to read, "It has been more than 49 days (7 weeks) since your last menstrual period began." We recognize that the other bullets begin "You," and that parallelism is preferable, but the phrasing FDA proposed is not an accurate statement of the women for whom Mifeprex can appropriately be prescribed.

11. Under "Who should not take Mifeprex?", we have also deleted the second sentence of the seventh bullet, so that this bullet, like the others in this section, provides clear and direct information about specific issues, without more detailed explanation.

12. Under "How should I take Mifeprex," we have deleted the first sentence ——— because it is confusing in light of the other sections of the Medication Guide which correctly advise that the mifepristone regimen only works 92-95% of the time. Also, we have:

a. Added the phrase "Read this Medication Guide" as the first item under the first bullet (Day 1).

b. Reversed the order of your third bullet so that making the decision about taking Mifeprex precedes the signature on the PATIENT AGREEMENT.

c. Revised the seventh bullet. As stated in the prescribing information, the prescriber

is supposed to give the patient misoprostol unless abortion has occurred. That is not the same thing as checking to see whether she is still pregnant, so we have conformed the Medication Guide to the package insert.

d. Revised the eighth bullet to delete the word [redacted] It is not appropriate to suggest that [redacted] so we have substituted the phrase FDA has previously chosen, "to be sure you are well."

e. In the ninth bullet, we have deleted the phrase, [redacted] for the reason given in Item 5, above.

13. Under "What should I avoid while taking Mifeprex and misoprostol," we have revised the breastfeeding language so that the woman is advised to "discuss" the issue with her provider, rather than asking and, implicitly, doing what she is told.

14. Under "What are the possible side effects of using Mifeprex," we have deleted the agency's definition of heavy bleeding and substituted the current standard definition: " . . .if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours . . ."

15. We have deleted [redacted] and substituted language reflecting what we think is the concern here, "When should I begin contraception?" Also, we have added at the end of the second sentence the phrase you previously suggested , "or before you start having sexual intercourse again."

PATIENT AGREEMENT

We have conformed the PATIENT AGREEMENT to the Medication Guide as we have revised it.

* * *

We look forward to your response to this letter, to resolving the remaining issues, and to the approval of the NDA for Mifeprex.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

APPEARS THIS WAY
ON ORIGINAL

UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

EASTMAN DENTAL CENTER
SCHOOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING
STRONG MEMORIAL HOSPITAL
UNIVERSITY MEDICAL FACULTY GROUP

DEPARTMENT OF FAMILY MEDICINE
UNIVERSITY OF ROCHESTER/HIGHLAND HOSPITAL

9-1-00

TO: _____

FROM _____

IND - _____

From. _____

INTERNET - CALL FOR MIFEPRISTONE

spected DOCTORS

e are pleased to inform you that we will start selling 200MG
25MG
IFEPRISTONE tablet dose along with misoprostol From 1
ptember 2000 onward.

ee 1 mind possiablity's of longterm association with
ou Doctors/Hospital's in various country's we are
ving a purposal which as below:-

ne selling price for Mifepristone tablet/dose will be same as
evailing in purchaser' country but they will get 15 to 25%
scount in form of free products such as pregnancy test/Lh
ulation/FSH/OTHER cassette/strip and or tibolone / other
&g segment tablet/ capsule/injection.(In This regard we are
ending our products list by SEPERATE E-MAIL)

lease advise prevailing price of mifepristone in your country
s well as how many tablet/dose you can buy at a time enabling
s to give you our best (15 to >25% free product discount).If
ossiable please send us contact information of known O&G
octors/hospital either in your country or in other country's
ND ALSO CONTACT INFORMATION OF O&G DOCTORS ASSOCIATION IN
OUR COUNTRY/ANY OTHER
OUNTRY'S.

ooking forward to your reply
est regards
ILIP CHOUDHURY
IVERSIFIED CORP.,
NDIA

Jacob W. Holler Family Medicine Center
885 South Avenue
Rochester, New York 14620
(716) 442-7470 Fax: (716) 442-8319

NDA 20-687

INFORMATION REQUEST LETTER

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

AUG 30 2000

Dear Ms. Arnold:

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

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

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

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

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

Sincerely,

/S/ 8/30/00

————
————Project Management Staff
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments

APPEARS THIS WAY
ON ORIGINAL

NDA 20-687

INFORMATION REQUEST LETTER

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

Dear Ms. Arnold:

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

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

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

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

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

Sincerely,

[redacted]

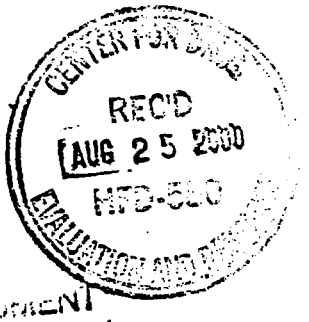
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments

APPEARS THIS WAY
ON ORIGINAL

Danco Laboratories, LLC

August 24, 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

DRUG AMENDMENT

BC

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 a ——— 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,

/S/

President and Chief Executive Officer

/dns
Enclosure

APPEARS THIS WAY
ON ORIGINAL

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 ———

Danco Laboratories, LLC

August 21, 2000

ORIGINAL

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 200mg Oral Tablets

- Amendment 055 - Submission of Additional Testing and Stability Data on Post Process Adjustment Drug Substance

Dear ———

Consistent with the commitments made in Amendment 050 dated July 5, 2000 and Amendment 052 dated July 13, 2000, this Amendment 055 provides additional information on mifepristone Drug Substance manufactured by the adjusted process, which was described in Amendment 048, dated June 22, 2000. As we have previously discussed with ——— this additional information is intended to establish a link between the pre process adjustment and post process adjustment Drug Substance.

A- Post Process Adjustment Drug Substance Stability Data

As per our commitment in Amendment 052, we are now providing the six-month accelerated and long-term stability data on one post process adjustment Drug Substance batch #000105 (see Attachment A-1). These data show that there are no significant changes or trends from the zero time data after six months under either accelerated or long-term storage conditions. The results continue to be consistent with the results observed in both the accelerated and long-term studies on pre process adjustment batches.

In addition, consistent with our commitment in Amendment 052, we are also providing the two-month accelerated stability data on three post process adjustment Drug Substance batches #000501, #000502 and #000503 (see Attachment A-2). Again,

these data show consistency with previously reported stability data on the pre process adjustment Drug Substance batches. As previously agreed, the three-month and six-month accelerated stability data on Drug Substance batches #000501, #000502 and #000503 will be reported to the FDA when the data becomes available.

B. Dissolution Data on Drug Product made from Post Process Adjustment Drug Substance

As per our commitment in Amendment 050, we have manufactured a production batch of Drug Product (#20001) using post process adjustment Drug Substance. Tablets from this Drug Product batch have been subjected to a S-2 level dissolution study. These data (see Attachment B-1) show that dissolution results for Drug Product batch #20001 are comparable to the results previously obtained for Drug Product batch #99007 made from pre process adjustment Drug Substance (see Attachment B-2). We have presented below a summary table of data comparing Drug Product batch #20001 to Drug Product batch #99007.

Comparison of Dissolution Studies on Drug Product Made from Pre and Post Process Adjustment Drug Substance

Drug Product Lot. No.		99007			20001		
Drug Product Manufacture Date		October 1999			August 2000		
Drug Substance Lot No. Used		990103 (pre process adjustment)			991006 (post process adjustment)		
Drug Product Dissolution Rate Profile	Time (Min)	—	—	—	—	—	—
	Mean %	97	103	105	98	101	102

Overall, the additional results reported in this amendment continue to support our conclusion in Amendment 052 that the pre and post process adjustment Drug Substance are comparable and that either is acceptable for use in manufacturing finished Drug Product.

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

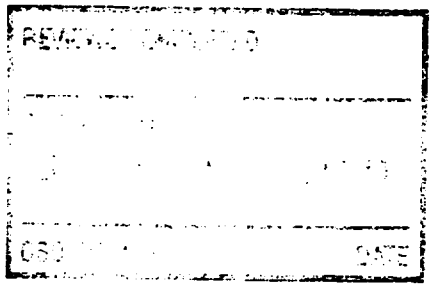
Sincerely,

/s/

President and Chief Executive Officer

/dns
Enclosure

cc: Sandra P. Arnold – Population Council



MIF 001355

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 21 2000

The Honorable Tom A. Coburn, M.D.
House of Representatives
Washington, D.C. 20515-3602

Dear Dr. Coburn:

Thank you for your letter of June 16, 2000, to the Secretary, Department of Health and Human Services, regarding the appointment of Dr. Susan Allen as Director, Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration (FDA). The Secretary has asked us to respond directly to you.

The following are your specific questions, followed by our responses:

Question 1: Who made the decision to hire Susan Allen?
Question 2: Who made the decision to put Susan Allen in charge of FDA's Reproductive and Urologic Drug Products Division?

Dr. Allen's hiring followed standard hiring practices. Dr. Allen responded to a vacancy announcement for the position of the Director of the Division of Reproductive and Urologic Drug Products, CDER. She, along with several other candidates, was interviewed by two teams of her peers. These teams consisted of staff from CDER, both from within the Division of Reproductive and Urologic Drug Products and external to it. The final decision was based on input from both teams. The final authority for hiring decisions for all Division Directors in the Office of Review Management, CDER, is the Deputy Center Director for Review Management.

Question 3: What role will the FDA's Reproductive and Urologic Drug Products Division have in determining the final approval/disapproval of the marketing application for mifepristone?

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Dr. Allen, a recognized expert in reproductive health, was selected for the position of Director of the Division, following the process described in the responses to Questions 1 and 2 above, because she was believed to be the best candidate.

We appreciate your concern about conflicts of interest that may be present when FDA employees face matters related to their previous employment or other experiences, and we wish to assure you that there are Standards of Ethical Conduct for all employees of the Executive Branch that assure the impartiality of the staff in performing their official duties.

We hope this information address the concerns raised in your letter. If we can provide additional assistance, please let me know.

Sincerely,

/s/

for Legislation

Enclosure

APPEARS THIS WAY
ON ORIGINAL

STANDARDS OF ETHICAL CONDUCT FOR EMPLOYEES OF THE EXECUTIVE BRANCH

Including:

Part I of Executive Order 12674

and

5 C.F.R. Part 2635 Regulation

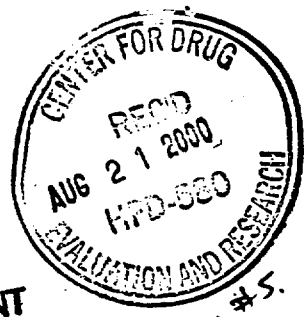
Prepared by:
United States Office of Government Ethics
Suite 500, 1201 New York Avenue, NW.
Washington, DC 20005-3917

August 1992

Danco Laboratories, LLC

August 18, 2000

ORIGINAL



ORIG AMENDMENT

- See Chem. Rev #5.

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

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

Dear ———

Per your discussion with Nancy Buc, I am enclosing our preliminary response to the Form 483 Inspectional Observations issued at the conclusion of the recent inspection of our Drug Substance plant. This response was sent initially on August 10 to ——— ——— Compliance Officer.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

cc: Sandra P. Arnold – Population Council
——— – FDA
——— FDA (no enclosure)

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

GCF-1
cc:

Food and Drug Administration
Rockville MD 20857

August 11, 2000

Ralph Hale, M.D.
Executive Vice President
The American College of Obstetricians
and Gynecologists
409 12th Street, S.W.
Washington, D.C. 20024-2188

E. Ratcliffe Anderson, Jr., M.D.
Executive Vice President, CEO
American Medical Association
515 North State Street
Chicago, IL 60610

Dear Drs. Hale and Anderson:

Thank you for your letter of July 24 expressing concerns about proposed restrictions for the distribution and administration of mifepristone and requesting a meeting with me and my staff to discuss these issues. We also appreciate receiving the copy of your analysis of possible mifepristone restrictions, and have provided a copy of it to staff in the Center for Drug Evaluation and Research.

At my request, [redacted] tried to contact you to respond to your request to meet. Her office routinely answers requests of this nature. Unfortunately, she was unable to reach Dr. Hale by phone, but in an effort to make contact expeditiously, did send an e-mail, which we hope has been received.

Since your request was to meet with me, I want to be clear that I frequently meet with officials from health organizations as well as advocacy groups in various forums to discuss broad scientific and policy issues that affect the Agency. However, I have made it a practice not to meet with outside organizations or their representatives to discuss a product that is actively under review by the Agency. I believe this approach safeguards the integrity of the product review process the FDA is mandated to conduct and all who are subsequently affected by the final decision on a product undergoing review.

We recognize that you believe strongly that a meeting is appropriate to present your views. As [redacted] mentioned in her e-mail, she and representatives from FDA's Office of Women's Health, are willing to meet and listen to your concerns since they are not in the product review division. They will not be able to discuss with you any

specifics under consideration about mifepristone. These discussions are appropriately taking place between the FDA and the sponsor of the new drug application.

We can assure you that the Agency's decisions on this application, as on all others, will be made based on sound science and on whether the products are safe and effective for the patients who will use them.

Thank you for sharing your concerns. I look forward to working with ACOG and AMA in the future on important public health issues of mutual interest.

Sincerely,

Jane E. Henney, M.D.
Commissioner of Food and Drugs

APPEARS THIS WAY
ON ORIGINAL

July 24, 2000

Jane Henney, M.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

The undersigned organizations, representing 340,000 physicians, are very concerned about restrictions we understand the Food and Drug Administration (FDA) has proposed for distribution and administration of the drug mifepristone.

We understand that the FDA has proposed at least five restrictions on access to the drug. These requirements are not based upon scientific facts, do not follow current medical practice, and impose inappropriate conditions on the practice of medicine.

We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely free from any political influence.

Thank you for your interest in this important issue. We look forward to meeting with you and your staff at your earliest opportunity to discuss our concerns in greater detail.

Sincerely,

Ralph W. Hale MD

Ralph Hale, MD
Executive Vice President
The American College of Obstetricians and Gynecologists

E. Ratcliffe Anderson, Jr., MD
Executive Vice President
American Medical Association

APPEARS THIS WAY
ON ORIGINAL

00-4974

ROUTING HISTORY
DATE: AUG 02, 2000

FDA Control Number: 00 4973 Tracer #: OS #:

Date of Correspondence: 07/24/00 Date Into FDA: 08/02/00

To: JANE E HENNEY HF-1

From: RALPH W HALE, THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

Synopsis: ENCLOSES THE AMERICAN COLLEGE OF OBSTETRICIANS & GYNECOLOGISTS' ANALYSIS OF POSSIBLE FDA RESTRICTIONS ON MIFEPRISTONE

Lead Office: HFD-1 Home Office: HF-40

Contact/Phone#: [redacted]

Date Due Out of FDA: 08/16/00 Closed Date: OPEN

Copies: GENERAL DISTRIBUTION
HF-1 JANE E HENNEY
HF-40 [redacted]
HF-10 [redacted]
HF-40 [redacted]

Coordination:

Signature Required:

Assigned By	Assigned To	Referred Act	Status
HF-40	[redacted] HFD-1	08/02/00 DR	Referred 08/02/00

Remarks: PLEASE SEND COPY OF RESPONSE TO [redacted], HF-40. SEE ALSO TRAC #00-4974

APPEARS THIS WAY
ON ORIGINAL

July 24, 2000

Jane Henney, M.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Henney:

Enclosed please find the American College of Obstetricians & Gynecologists' Analysis of Possible FDA Mifepristone Restrictions.

I have also sent a letter with E. Ratcliffe Anderson, Jr., MD of the American Medical Association that touches our joint concerns with the proposed restrictions and requests a meeting with you.

Thank you for your interest in this important issue.

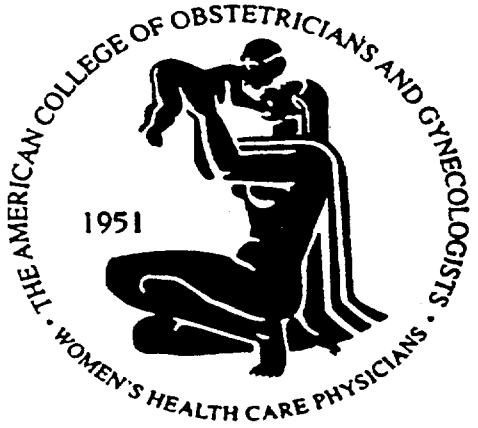
Sincerely,

Ralph W. Hale MD

Ralph Hale, MD
Executive Vice President
The American College of Obstetricians and Gynecologists

APPEARS THIS WAY
ON ORIGINAL

00-4973



American College of Obstetricians and Gynecologists

Analysis of the Possible FDA Mifepristone Restrictions

July 27, 2000

FDA Proposal 1: Distribution and use of the drug would be limited to only licensed physicians.

a. Prohibiting the prescription, dispensing, or use of the medication by anyone other than licensed physicians interferes with state medical, pharmacy, and nursing scope of practice laws. These laws, not the FDA, determine which professionals are allowed to prescribe and dispense medications within each state. There is no reason to treat this drug as a controlled substance. There are many other medications, some of which are abortifacients, that are available through prescription to a pharmacy.

b. Marketing mifepristone directly to physicians or facilities rather than through pharmacies may be a reasonable way that the company would choose to begin marketing this drug. However, a requirement to do so by the FDA will be difficult to change and may restrict wider distribution in the future.

c. Any information about physician offices, pharmacies, hospitals, or any other facilities that receive the drug must remain strictly confidential in order to protect those who use the drug from anti-abortion violence. Any government requirement that would result in a list would immediately place those who provide the drug in jeopardy.

FDA Proposal 2: The physician must be "trained and authorized by law" to provide surgical abortion.

Requiring that a physician be trained as a provider of surgical abortion is not necessary to administer mifepristone correctly and safely. Nor is such training necessary to treat spontaneous abortion. Requiring certification of this training does not reflect current medical practice. In fact, there is no method to certify physicians as surgical abortion providers or for any other type of surgery. Responsibility for certification of medical

professionals in this case rests with state licensing boards and the American Board of Obstetrics and Gynecology, a professional body established for this purpose.

FDA Proposal 3: The physician must have "certification" for ultrasound dating of pregnancy and detecting ectopic pregnancy.

a. Requiring ultrasound to date a pregnancy or determine if there is an ectopic pregnancy is not required to administer the drug safely and correctly. Physicians and patients can quite accurately date a woman's pregnancy.[1]

b. Currently the American Institute of Ultrasound in Medicine (AIUM) and the American College of Radiology, which are the only certifying bodies for ultra-sound in the United States, do not certify physicians to provide specific ultrasound procedures, including dating pregnancies and detecting ectopic pregnancies. Furthermore, ultrasound certification is controversial, with implications for third party reimbursement issues, and is not related to prescribing this drug.

FDA Proposal 4: Distributing physicians must be certified to provide mifepristone through a curriculum approved by the FDA.

Requiring special training is also not necessary to safely administer mifepristone. Evidence from the clinical trials is unequivocal in demonstrating the drug's safety and efficacy as the FDA approvable letter states. Further, the FDA is not an educational institution and has no mechanism in place to develop medical curricula.

[1] Ellertson, Charlotte, et al. "Accuracy of assessment of pregnancy duration by women seeking early abortions." *THE LANCET* March 11, 2000: 355: 877-881.

FDA Proposal 5: Prescribing physicians must have admitting privileges at a hospital within an hour of the offices where the drug is dispensed or administered.

Privileges at a hospital are not necessary for prescribing mifepristone safely. The complication rates for mifepristone are very low, with a small number of patients requiring emergency room care or hospitalization. The April 30th, 1998, New England Journal of Medicine article, "Early Pregnancy Termination with Mifepristone and Misoprostal in the United States," states that only 2% of women using these drugs required hospitalization, underwent surgical intervention, or received intravenous fluid.[2] Another New England Journal of Medicine article states, "This regimen appears to be as safe as surgical abortion performed under the safest conditions."[3]

The prescribing physician does not need to be in the emergency room or to be the admitting physician if a patient requires follow-up emergency care. Women experiencing miscarriages and spontaneous abortions frequently require the same services and care and appropriately receive this care at their physicians' offices.

The FDA has imposed no similar requirements on drugs that are far more likely to cause complications requiring emergency care. This requirement discriminates against physicians in rural areas, and creates a significant barrier to access for women in these areas.

---

[2] Spitz, I.M. et al. "Medical termination of pregnancy." *New England Journal of Medicine* 1998: 338: 1241-1247.

[3] Spitz, I.M., Bardin, C.W. "Mifepristone (RU486): a modulator of progestin and glucocorticoid action. *New England Journal of Medicine* 1993: 329: 404-412.

Issue

Controversy continues over importation of RU-486

Background

RU-486 is an abortion-inducing drug manufactured by the French company Roussel Uclaf. The drug is approved in France, England, and Sweden. The manufacturer has not submitted a new drug application to FDA seeking approval in the United States.

In 1989, FDA issued an import alert, stating as guidance to FDA employees that RU-486 would be inappropriate for release under the personal use importation policy. In July 1992, after FDA and the Customs Service detained a small quantity of RU-486 from a woman who was entering the U.S., a class action lawsuit was filed on behalf of all women who want to import the drug for personal use as an abortifacient. Benten v. Kessler (E.D.N.Y.). District Judge Charles Sifton issued a preliminary injunction directing FDA to release the drug to plaintiffs. The court ruled that the import alert was promulgated without notice and comment rulemaking, in violation of the Administrative Procedure Act and FDA regulations. The court also found that FDA's action was an arbitrary and capricious change from the agency policy permitting importation of some drugs for personal use, such as AIDS drugs.

The Second Circuit Court of Appeals stayed the preliminary injunction. On July 17, the Supreme Court refused to vacate the stay, concluding that plaintiffs had failed to demonstrate a substantial likelihood of success on the merits of their claim that rulemaking was required. The Second Circuit thereafter granted the government's unopposed motion to dismiss the appeal as moot and to vacate the district court's decision.

Status

The government has moved to dismiss the case in district court on grounds of mootness, failure to exhaust administrative remedies, and lack of jurisdiction. Plaintiffs have moved for summary judgment, arguing APA and constitutional violations. A hearing is scheduled for June 3, 1993. On January 22, 1993, President Clinton directed the Secretary to instruct FDA to assess the evidence concerning whether RU-486 is appropriate for personal use importation and whether the import alert should be rescinded. On February 24, FDA met with Roussel Uclaf, which emphasized the importance of finding a way to make the drug available in the U.S. without the direct involvement of the company (e.g., a U.S. drug firm, a research center, or a university).

Contact Person

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)* 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 001371

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

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306(k)(1))
☐	17. Field copy certification (21 CFR 314.50(k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Documentation for FDA Meeting on August 4, 2000.

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Sandra Arnold	Sandra P. Arnold, Vice President	07/27/2000

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
One Dag Hammarskjold Plaza, New York, New York 10017	(212) 339-0663

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

MIF 001372

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

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

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

As you will see as you proceed through this letter, we propose two subjects for inclusion in a black box warning. First, we suggest that the physician be advised to plan for and organize

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

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

2 and 8. Physician Training

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

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

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

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

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

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

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

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

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

We also want to remind you that the proposed labeling

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

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

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

Recognizing that a woman who chooses to take her misoprostol at home may find herself with questions, we have also revised the labeling to focus on that point in the process. First, under DOSAGE AND ADMINISTRATION, Day Three: Misoprostol Administration, we have added to the end of the second paragraph the following sentence: '

Similarly, we have revised the second bullet under How Should I Use Tradename in the PATIENT INFORMATION to add a new second sentence:

A similar sentence

') is already included in the What Are the Possible Side Effects of Using "Tradename" section of the PATIENT INFORMATION and in the 6th bullet of Information for Patients in the prescribing information.

10. Incidence of Need for Curettage

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

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

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

13. Timing of Dose of Misoprostol

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

16 and 33. Contraception

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

17. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

26. Provider Qualifications

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

provider qualifications ——————————→ We continue to believe that change is not only unnecessary, but also in fact potentially counterproductive for patients.

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

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

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

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

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

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

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

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

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

34. PATIENT AGREEMENT

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

- I understand that I will take "Tradename" in my health care provider's office.
- [redacted]

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

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

Encouraging and Documenting Provision of Information to Patients

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

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

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

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

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

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

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

* * *

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

Very truly yours.

Sandra Arnold

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT A: Exhibit E of the Distribution Plan, Prescriber's Letter/Order Form

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT B: Marked and Unmarked Labeling

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT C: Articles Regarding Home Use

APPEARS THIS WAY
ON ORIGINAL