Phase IV Studies of Mifepristone

Study II

Study of Ongoing Pregnancies

I. Introduction

In extremely rare instances, mifepristone-misoprostol may fail to terminate a pregnancy and women may not have the recommended surgical abortions at their follow-up visit. In Europe where about 410,000 women have been treated with mifepristone or mifepristone-misoprostol during the last decade, there were 82 reported cases of ongoing pregnancy. Among those cases, only 26 women are known to have carried their pregnancies to term. There are no reports of birth defects among these 26 live births. Only one case of a congenital malformation was reported in a fetus that was subsequently aborted.

II. Objective

To determine the outcome of these rare ongoing pregnancies, we have developed a surveillance, reporting, and tracking system in the U.S. This system will allow us to investigate the maximum number of ongoing pregnancies and to document any reports of fetal malformation.

III. Study Design, Materials, and Methods

A. Study Approach

This surveillance study will record and investigate all reported cases of ongoing pregnancies after mifepristone-misoprostol becomes available in the U.S..

B. Data Source

All cases of ongoing pregnancies in the U.S. reported to the Medical Director of Danco Laboratories will be included in our database.

C. Inclusion and Exclusion Criteria

Providers will be instructed to report to the Medical Director at Danco Laboratories all cases in which women have an ongoing pregnancy after taking mifepristone and decline to terminate the ongoing pregnancy. These cases will be included in the study. Women who have an ongoing pregnancy at the time of their follow-up visit and who receive a surgical termination at that time, as per the standard protocol, will not be included.

D. Data Collection Methods

Prior to receiving mifepristone, all providers of the drug in the U.S. must agree in writing on the Prescriber's Agreement to report all cases of ongoing pregnancy to the medical director at Danco Laboratories, LLC. All reported cases of ongoing pregnancy will be entered into a database.

Once a case of an ongoing pregnancy has been reported, the Medical Director of Danco Laboratories will immediately contact the woman's health care provider. To preserve the woman's right to privacy and confidentiality, the woman's health care provider will contact the woman and ask if she is willing to be included in a study to determine the outcome of ongoing pregnancies. If the women refuses to be enrolled, her case will remain in the database and the outcome of the pregnancy will be entered as "unknown." If the woman agrees to participate, the woman's health care provider will send the Danco Medical Director her contact information.

The Medical Director will then give her contact information to the research staff at the Population Council who will contact her directly and document the current status of her ongoing pregnancy. If the woman still has a viable ongoing pregnancy, the researcher will continue to follow her until the pregnancy ends in one of the following ways: 1) delayed spontaneous abortion, 2) delayed induced abortion (normal fetus), 3) delayed induced abortion (abnormal fetus), 4) stillbirth 5) live birth (normal infant), and 6) live birth (abnormal infant). All reported malformations will be documented and assessed for their possible association with mifepristone.

In addition, any spontaneous reports in the U.S. of live births of children exposed to mifepristone *in utero* will be investigated and any abnormalities will be recorded.

All data on ongoing pregnancies will be summarized and submitted annually for the next five years to the FDA. Depending on the results from these data, we will assess whether continued surveillance is necessary.

E. Defining Outcome Variable

This study will primarily document the number of ongoing pregnancies after exposure to mifepristone in the U.S. By investigating the reports of ongoing pregnancies, it will determine the outcome of such pregnancies as one of the following: 1) delayed spontaneous abortion, 2) delayed induced abortion (normal fetus), 3) delayed induced abortion (abnormal fetus), 4) stillbirth 5) live birth (normal infant), and 6) live birth (abnormal infant).

F. Defining the Main Independent and Confounding Variables

Since the regimen for medical abortion consists of taking two drugs, mifepristone and misoprostol, it will be very difficult to disentangle the separate effects of the two drugs on fetal development. There is no evidence to suggest that exposure to mifepristone *in utero* causes any minor or major birth defects. In contrast, although alleged teratogenic effects of misoprostol have not been conclusively documented, several anecdotal reports from Brazil suggest that misoprostol may be associated with certain congenital abnormalities such as Möbius syndrome. In addition, the women may also have taken other drugs or substances to induce abortion. Finally, as all pregnancies carry an inherent risk of fetal malformation, it will be difficult to distinguish between drug related and non-drug related birth defects.

G. Analytical Plan

Based on the European experience, we expect that the incidence of ongoing pregnancies will be extremely rare. We would anticipate at most 5 to 10 ongoing pregnancies per year. Moreover, we expect that the number of ongoing pregnancies carried to term will be much lower; maybe 1 or 2 per year. Given this tiny sample size we will need to run the study for several years to achieve a reasonable sample size. Even then the sample is likely to be too small to be able to make any meaningful comparisons with the normal incidence of birth defects.

H. Strengths, Limitations and Biases

This study will track the outcomes of ongoing pregnancies after exposure to mifepristone and mifepristone-misoprostol. Although we anticipate very few cases of ongoing pregnancy, we recognize the importance of monitoring ongoing pregnancies to verify that exposure to mifepristone or mifepristone-misoprostol does not increase the risk of birth defects or of a particular type of birth defect.

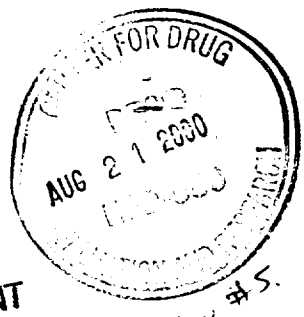
The main limitation of the study is the sample size. This drawback is unavoidable. Since we will also include spontaneous reports of ongoing pregnancies from women, it is possible that we will double count some ongoing pregnancies. We will attempt to avoid this error by ascertaining the names and home addresses of as many women as possible and checking for duplications.

This sample is likely to be biased since outcomes of congenital malformations in either an aborted fetus or a live birth are more likely to be reported than normal fetuses or infants.

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 ———

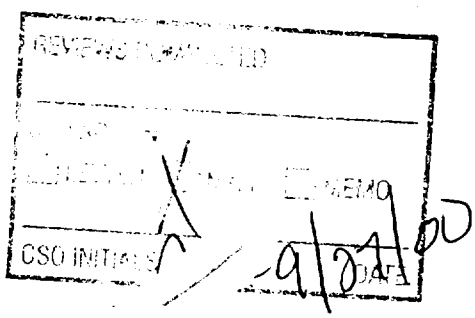
Per your discussion with Nancy Buc, I am enclosing our preliminary response to the Form 483 Inspectional Observations issued at the conclusion of the recent inspection of our Drug Substance plant. This response was sent initially on August 10 to ———

Sincerely,

President and Chief Executive Officer

/dns
Enclosure

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



This document constitutes trade secret and confidential commercial information e ..mpt 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 ———

COPY

[redacted] Compliance Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality, HFD-322
7520 Standish Place, Room [redacted]
Rockville, MD 20855

August 10, 2000

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: July 24-28, 2000
Inspectional Observations (Form FDA 483): Corrective Action

Dear [redacted]

On behalf of our principals, we are herewith enclosing a preliminary response to the Inspectional Observations issued at the conclusion of the recent inspection of their plant.

A desk copy has been sent to [redacted] and [redacted] for their review.

A complete response, including evidence of the completed corrective action or of corrective action underway, will be submitted before the end of this month.

Thank you for your attention.

Sincerely,

[/S/]

President

[redacted]

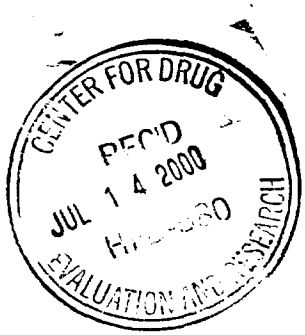
Encl.

cc: [redacted] Investigator, U.S.F.D.A., D.E.I.O., Rockville, MD
[redacted], U.S.F.D.A., Kansas City District Office
[redacted], Manufacturing, Danco Investors Group, L.P.
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

Danco Laboratories, LLC

July 13, 2000

Received
9/27/00



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

ORIG AMENDMENT
BC

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

- Amendment 052 - 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 this Amendment 052 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 Physical and Analytical Data

As per our commitments in Amendment 050, we are providing certain physical and analytical data on three batches of post process adjustment Drug Substance. The batches tested are #000501, #000502 and #000503.

1- graphs (See Attachment 1)

The curves of the graphs for all three batches appear comparable to those previously generated from pre process adjustment batches reported in the original CMC submission, Amendment 025 dated June 3, 1999. There are no discernable differences in the structure of Drug Substance between pre and post process adjustment batches.

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2- [redacted] See Attachment 2)

The [redacted] for all three batches confirm that the post process adjustment Drug Substance batches consist solely of [redacted]

3- [redacted] (See Attachment 3)

The [redacted] for all three batches of Drug Substance appear to be clean, without any unusual peaks and consistent with pre process adjustment batches.

The following table summarizes comparative impurity data on three pre and three post process adjustment batches:

Comparative Impurity Data

	Pre process adjustment batches	Post process adjustment batches
[redacted]		

4- [redacted] See Attachment 4)

The [redacted] curves for all three batches show that the adjusted process yields Drug Substance well within the established [redacted]

The following table summarizes the comparative [redacted] data on three pre and three post process adjustment batches:

These results show the comparability of the [redacted] for pre and post process adjustment Drug Substance batches.

B. Post Process Adjustment Drug Substance Stability Data

As per our commitment in Amendment 050, we are now providing the three-month accelerated and long-term stability data on one post process adjustment batch, #000105 (See Attachment 5). These data show that there are no significant changes or trends from the zero time data after three months under either accelerated or long-term storage conditions. This is consistent with the results observed in both the accelerated and long-term studies on pre process adjustment batches, which are also included in Attachment 5.

Six month accelerated and long-term stability data for this batch #000105 is due by the end of July and will be reported to the FDA as soon as it is available during August. Furthermore, as we stated in Amendment 050, two month long term and accelerated stability data on three additional batches will be provided by the end of August followed by three-month data by the end of September. Additionally, a three batch accelerated stability study recently begun in the U.S. will provide three months data in mid-October.

In summary, we believe that all of the post process adjustment Drug Substance physical and analytical data presented in A above together with the post process adjustment Drug Substance stability data presented in B above demonstrate:

- the comparability and consistency of Drug Substance batches manufactured before and after the process adjustments and
- that Drug Substance from either the pre or post adjustment process is acceptable for use in manufacturing finished Danco Drug Product.

As per our commitment in Amendment 050, we plan to manufacture a production batch of Drug Product using post process adjustment Drug Substance within the next month. Tablets from this Drug Product batch will be subjected to a ——— dissolution study and we plan to report this data to the FDA by the end of August.

Separately, and in response ——— uestion concerning Drug Substance batch dating by the manufacture

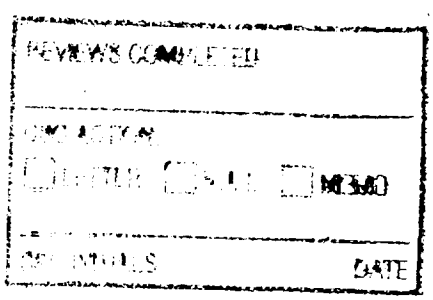
Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

/S/

President and Chief Executive Officer

cc: Sandra P. Arnold – Population Council



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 13, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*

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

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

APPLICATION INFORMATION

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

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

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

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

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

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

REASON FOR SUBMISSION

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

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

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

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

MIF 007909

Danco Laboratories, LLC

September 8, 2000

ORIGINAL

Reviewed
See Chemistry
Review.
9/19/00
ORIG AMENDMENT
BC

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 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

/dns
Enclosure

cc: Sandra P. Arnold – Population Council

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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 8, 2000
TELEPHONE NO. (Include Area Code) (212) 339-0663	FACSIMILE (FAX) Number (Include Area Code) (212) 980-3710
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: One Dag Hammarskjold Plaza, New York, New York 10017	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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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 007911

Danco Laboratories, LLC

noted 9/27/00

Received 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.

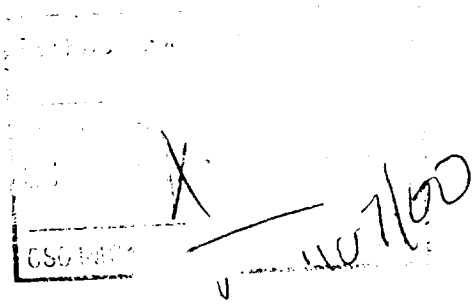
Please do not hesitate to contact me if you have any questions on the submitted material.

Sincerely,

President and Chief Executive Officer

/dns
Enclosure

cc: Sandra P. Arnold – Population Council



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Success by age for women with gestational age ≤63 days

Age	Success		Total
	No	Yes	
<25	99 (12.5%)	691 (87.5%)	790 (100.0%)
25-29	105 (17.5%)	495 (82.5%)	600 (100.0%)
30-34	60 (15.2%)	336 (84.8%)	396 (100.0%)
≥35	31 (13.5%)	198 (86.5%)	229 (100.0%)
Total	295 (14.6%)	1720 (85.4%)	2015 (100.0%)

Note: Pearson Chi-Square = 0.071, which is not significant at the 0.05 level.

Success by age for women with gestational age ≤49 days

Age	Success		Total
	No	**Yes**	
<25	18 (6.2%)	272 (93.8%)	290 (100.0%)
25-29	17 (6.8%)	234 (93.2%)	251 (100.0%)
30-34	18 (10.0%)	162 (90.0%)	180 (100.0%)
≥35	12 (11.3%)	94 (88.7%)	106 (1000%)
Total	65 (7.9%)	762 (92.1%)	827 (100.0%)

Note: Pearson Chi-Square = 0.222, which is not significant at the 0.05 level.

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

September 22, 2000

NEW CORRESP

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

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

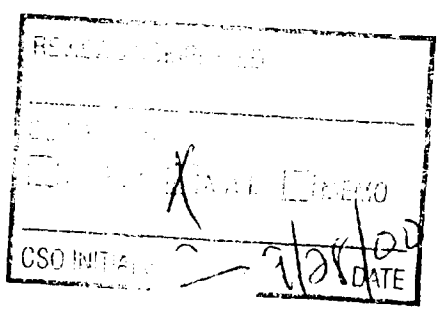
Dear

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

Sincerely,

Sandra P. Arnold

Sandra P. Arnold



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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

September 22, 2000

NEW CORRESP

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

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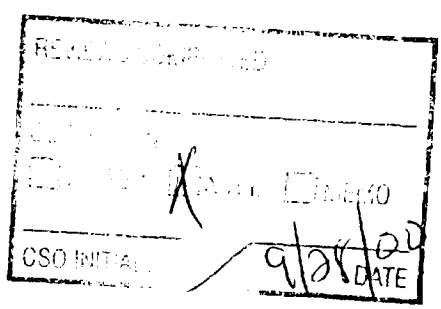

MIF 007915

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

Population Council

BEST POSSIBLE COPY

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

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

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Amendment 065; Revision to Prescriber's Agreement

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Sincerely,

Sandra P. Arnold

Sandra P. Arnold

/S/

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

ORIGINAL

September 26, 2000

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

ORIG AMENDMENT

Re: NDA 20-687, Mifepristone 200 mg Oral Tablets;
Amendment 066; Revision to Package Insert

Dear

I am enclosing a revised package in t. In accordance with telephone discussions on September 25, it revises the second sentence der Table 2 so that " . is replaced by " . . .have been reported after exposure during the first trimester."

Sincerely,

Sandra P. Arnold 9/26

Sandra P. Arnold

X 9/28/00

MIF 007917

One Dag Hammarskjold Plaza, New York, New York 10017

20687

Population Council

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

Sandra P. Arnold
Vice President
Corporate Affairs

FACSIMILE TRANSMISSION

September 26, 2000 ORIGINAL

Please deliver to: _____ (f) _____ (t)

From: Nancy L. Buc (202) 736-3608 (f) (202) 736-3610 (t)
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Total Pages (including cover sheet): 4

NIC

COMMENT:

9/26/00

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

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

9/26/00

Dear

10 copies will be delivered tomorrow, ~~#~~ the original certification signed by Ms. Arnold.

Nancy L. Buc

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

September 26, 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 067; Post-approval Commitments; Debarment Certification

Dear

We agree to submit the protocols for the Phase IV studies within 6 months of approval of this NDA. I am attaching an updated debarment certification statement.

Sincerely,

Sandra P. Arnold

Sandra P. Arnold

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

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

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

September 26, 2000

NEW CORRESP

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

Re: NDA 20-687, Mifepristone 200 mg. Oral Tablets;
Amendment 067; Post-approval Commitments; Debarment Certification

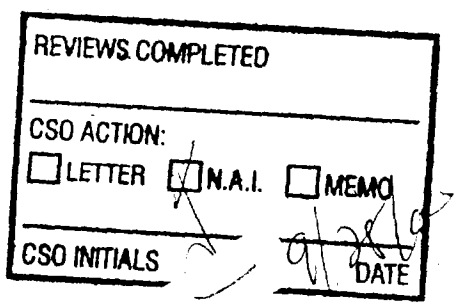
Dear

We agree to submit the protocols for the Phase IV studies within 6 months of approval of this NDA. I am attaching an updated debarment certification statement.

Sincerely,

Sandra P. Arnold 9/28/00

Sandra P. Arnold



One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710

Mifepristone
NDA No. 20-687

GENERIC DRUG ENFORCEMENT ACT OF 1992
CERTIFICATION STATEMENT

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

Signed: Sandra Arnold Date: 9/26/00

SANDRA ARNOLD, VICE PRESIDENT

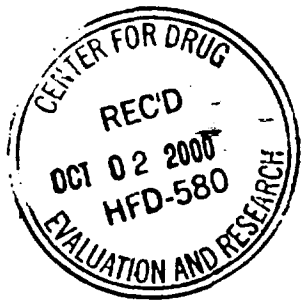
The Population Council

N 20-687

Danco Laboratories, LLC

VIA FACSIMILE: 301-594-6197

ORIGINAL



September 25, 2000

Center for Drug Evaluation
and Research
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

NEW CORRESP

Dear

Pursuant to your discussions this morning with
I wish to advise that Danco Laboratories, LLC:

- Has never heard of
- Has not used or any purpose in connection with any product of Danco
- Has no plans to utilize the services of in the future

Separately, we expect to import drug substance approximately

Sincerely,

President and Chief Executive Officer

/dns

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

Population Council

ORIGINAL

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

ORIG AMENDMENT

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

CSO

9/28/00
DATE

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

Danco Laboratories, LLC

August 21, 2000

ORIGINAL

Reviewed 9/27/00

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

ORIG AMENDMENT AUG 2000

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,

President and Chief Executive Officer

/dns
Enclosure

cc: Sandra P. Arnold – Population Council

FAX COVER SHEET

DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

Date: September 27, 2000

To: Nancy Buc

Phone: 202-736-3600 **Fax:** 202-736-3608

From:

No. of Pages without coversheet: 2

Phone: Enforcement and Surveillance (HFD-42)

Fax:

Comments:

Population Council

October 21, 1999

The Danco Group

[ ]

VIA FAX: 9-424-1952

Dear !

On August 30, 1994, the Population Council received from Roussel Uclaf mifepristone 200 mg tablets in polyethylene bag (bulk), Batch No. JMP 25524-109, Date of manufacture = July 1994, Expiration Date = July 1997. These tablets were stored at the Population Council; in , in an air-conditioned facility with normal controls of laboratory temperature and humidity.

On September 22, 1994 the above mifepristone tablets were repackaged into nine (9) small bottles (amber plastic light resistant, 15-DR bottle) with ablets per bottle. On September 26, 1994 these bottles were hand delivered to the for Stability Testing at room temperature and at an accelerated condition each for 0, 2, 6 and 12 months testing.

On November 7, 1997 and November 10, 1997 a total of mifepristone tablets, respectively, were repackaged from the stored at the Population Council under the same conditions described above) into small amber bottles. Then on November 11, 1997, these bottles were sent to for Stability Testing at room temperature for extension of the July 1997 expiration date. performed stability tests on these tablets at 0, 6, 12, and 18 month intervals.

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

cc: S. Arnold

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

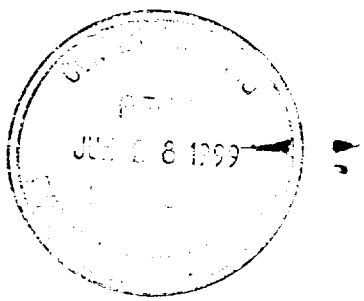
Population Council

ORIGINAL

ORIG AMENDMENT

June 25, 1999

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



Re: NDA 20-687, Mifepristone 200 mg Oral Tablets
Amendment 027 - Revised Physician and Patient Labeling

Dear

Per your request at our April 9, 1999 meeting with the FDA and in response to the NDA Approvable Letter from dated September 18, 1996, we are submitting revised physician and patient labeling for mifepristone. This letter describes our general responses to the FDA's requests and highlights the key changes we have made to our proposed labeling draft contained in NDA 20-687, submitted March 14, 1996. Although interim physician and patient labeling have been submitted previously to the FDA (Amendment 007 dated March 31, 1997, and Amendment 010 dated November 26, 1997), as you requested we are enclosing four copies of the revised labeling (Appendix A) and the proposed labeling, marked to show changes from the March 14, 1996 version (Appendix B). Many of the highlighted changes are due to the inclusion of the U.S. clinical trials data (previously submitted in Amendment 010, dated November 26, 1997 and submitted in final form in Amendment 024, dated June 3,1999).

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 for inspection or copying, or in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. § 20.45. Contact telephone number is

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

General comments

1. As requested, we have excerpted and incorporated sections from the approved labeling of misoprostol that are relevant for single-dose use as part of the mifepristone-misoprostol regimen.

2. We have obtained approval of the USAN Council for adoption of the name, mifepristone, and assurance that it complies with § 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (see Appendix C for the letter from the USAN Council dated February 25, 1998).

Black box warning

We propose that a black box warning is not necessary since there are no unusually dangerous consequences for any subsets of women. We do agree, however, that the information you note in this section is important, and we include it throughout our proposed labeling, where appropriate (with minor diction changes). In response to your first point, we have emphasized that administration of mifepristone must be under the supervision of a physician _____ (The exact wording is fully explained below under the first point in the "General subsection.") In response to the second point, the treatment procedure is contraindicated for women who do not have adequate access to a medical facility equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation rather than specifying that _____ (see "Contraindications" for further explanation of this wording). The treatment procedure is also contraindicated for those women who are unable to understand the effects of the treatment procedure or to comply with the regimen. As for the third point, we have noted that there is a small risk of excessive bleeding and of on-going pregnancy at the end of the treatment. We therefore stress throughout the label and particularly in the patient information section that women should contact their provider if they have any concerns or questions, that they should complete the treatment schedule, and return for a follow-up visit to confirm that their abortion is complete. We would be willing to discuss the issue of a black box further, if you desire.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Description

We have included the structure of mifepristone and have corrected the chemical name by replacing "B" with "β."

Clinical pharmacology

1. The success rates and timing of expulsion data from the pivotal studies and from the U.S. trials are now described in the proposed text, and summarized in Tables 1a and 1b, respectively. Please note that the success rate and expulsion times documented in Table 1a refer to women who took either zero, one or two dose(s) of misoprostol. As we documented in our efficacy analysis in the NDA (Vol. 89, p. 6), the second dose of misoprostol had no significant effect on efficacy or timing of expulsion. For this reason, patients who received two doses of misoprostol are analyzed together with patients who received only one dose.

2. We have reformatted the "Pharmacokinetics/Metabolism" subsection to include subsections titled "Absorption," "Distribution," "Metabolism," and "Special Populations."

[redacted]

Indications and usage

1. We have amended the third paragraph, although we modified your proposed wording to be consistent with further changes, which are fully explained below under the "Dosage and Administration" section.

2. We have deleted the first sentence of paragraph four as requested.

3. a) We propose to use a slightly stronger wording: "...fails to terminate a woman's pregnancy, [redacted] pregnancy termination by surgery must be recommended." Note that we use this same wording also in subsequent portions of the labeling where applicable.

b) We have added the reference you requested.

Contraindications

As is mentioned above, we now require patients to have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation, if necessary, during the period from the first visit until discharged by the administering physician, instead of specifying that women [redacted] of such facilities. We feel that this language is more appropriate, given that the issue we wish to address is the availability of appropriate medical facilities to the patient. In addition, in this section, and where applicable later in the labeling, we have modified the text to specify that the back-up facility must be equipped to provide "emergency treatment of incomplete abortion," rather than the narrower [redacted]" described in the previous draft.

Warnings

1. We have numbered the paragraphs as you request, and have preceded the paragraphs with the suggested subheadings.

2. a) In the bleeding subsection, we have revised the first paragraph as requested and have made the following additional changes. [redacted]

and we have clarified that prolonged bleeding lasted for 30 days or more [redacted] cases in the pivotal trials. We have also included data on bleeding from the U.S. trials. Furthermore, we have reordered the treatments for heavy bleeding to reflect their frequency of use in clinical practice.

b) We have incorporated quantitative information on the frequency of excessive bleeding treated with uterotonic medications, vasoconstrictor drugs, intravenous fluids, and blood transfusions.

c) Because the studies of bleeding in the ≤ 49 day timespan do not quantitate levels of blood loss or measure the decrease in blood count or hemoglobin concentration, we have removed this sentence. Instead, we have included a more general statement that the duration of bleeding increases as the duration of pregnancy increases.

We have also removed the last sentence of the cardiovascular events subsection to remove the reference to light headedness. The statement is not substantiated by the data.

Precautions

General subsection.

1. We agree in principle with your requested revision, but feel a more appropriate wording is that "administration must be under the supervision of a physician [redacted] We propose, instead, that supervising physicians [redacted] able to assess the gestational age of an embryo and to diagnose ectopic pregnancies, and with access to emergency medical facilities. Please note that we have used this preferred wording throughout the proposed labeling.

2. Except for the word [redacted] we have adopted your requested wording for the body of the paragraph. However, we have deleted the last sentence, [redacted] We are not proposing labeling for surgical abortion, and we must assume that physicians providing this procedure know how to take appropriate care of their patients with underlying cardiac conditions as well as of any other patients with special needs.

3. As requested, we have deleted the last paragraph of this section. We have not included the requested sentence on effectiveness of the treatment procedure based on timing of misoprostol administration,

[redacted] The previous assumption that the effectiveness of the treatment procedure might

be lower if misoprostol were administered more than two days after mifepristone administration was not based on clinical data.

Drug Interactions subsection.

[redacted]

Pregnancy subsection.

In the case of a drug indicated solely for the termination of pregnancy, a subsection setting forth special caveats for pregnant women is not meaningful. We understand that mifepristone is the first such drug to be approved in the United States and therefore the first to render this section inapplicable. We seek your guidance on how best to proceed, but our proposal is to state in this section that the drug is intended for use only by women who do not wish to carry their pregnancies to term and therefore that no studies of the effects on pregnant women who are not seeking abortions are possible.

As requested, we have included a concise discussion of the available information from rabbit studies and from human experience. We have summarized all the information available concerning outcomes of reported pregnancies that were on-going at the end of the treatment procedure with mifepristone alone or with mifepristone-misoprostol but where the women declined surgical termination at that time (Table 2).

Nursing Mothers subsection.

We incorporated most of your requested wording and have amended the proposed labeling accordingly. However, since we do not have any information suggesting that this treatment is harmful for nursing mothers or their infants, we propose that breast-feeding women should consult with their medical provider to decide if they should discard their breastmilk for a few days, rather than being excluded from treatment.

Pediatric Use subsection.

As requested this sentence reads, "Safety and effectiveness in pediatric patients have not been established."

Adverse reactions

In the first paragraph, we have added a sentence to clarify that the treatment regimen is intended to bring on the bleeding and cramping that necessarily accompany a medical abortion. For this reason, nearly all women will experience such reactions. In addition, we added a sentence to [redacted] prior to beginning the treatment procedure.

1. As requested, in place of the narrative, we have supplied Table 3a and Table 3b, which summarize the data from the pivotal and U.S. trials, respectively. You asked for the experience of women who took mifepristone alone to be presented separately from the experience of women who took mifepristone followed by misoprostol. We take your request to mean that you are interested in the adverse events that providers determined are possibly or probably related to mifepristone such as events that occurred during the two days after women take mifepristone but before they ingest misoprostol. These data are not readily available in the pivotal studies, although we did collect them in the U.S. trials and have presented these data in Table 3c. Throughout this section, as requested, we limit the narrative and the tables to those women whose gestational age was ≤49 days.

2. We have revised the narrative portion, as requested, to discuss only the more serious and more frequent adverse effects.

3. As requested, we have removed the reference to [redacted].

Dosage and administration

We have deleted instructions to [redacted] since there are no data to support these restrictions..

We have adjusted the label to provide women with the option of —— returning to the clinic for administration of misoprostol ———————— We are aware that drug labels do not usually specify the physical location of the patient for drug administration, however, we thought it would be useful to mention available options. Please refer to the attached Appendix D for a summary of the information supporting this option. We would be willing to discuss this option further, if you desire.

How supplied

1. We have added a brief description of the proposed distribution system, as requested.

2. We have supplied specific information regarding the tablet imprinting and carton contents.

Other

Information for Patients subsection.
In the paragraph about risk of future pregnancy, we have corrected our previous wording slightly for accuracy. This same corrected wording appears again later in the proposed labeling.

Carcinogenesis, Mutagenesis, Impairment of Fertility subsection.
We have added information from an additional animal study. This third study does not change the sense of the paragraph, but strengthens the point being made.

Throughout the proposed labeling, we have made minor modifications to add more precise language than that originally proposed. For example, we have revised and reorganized the Patient Information to simplify the language and clarify the presentation of this information. Similarly, we have checked all figures and adjusted numbers slightly where appropriate.

While all references have been previously provided in the March 14, 1996 submission and recently amended to include the U.S. clinical trials data (submitted in final form in Amendment 024, dated June 3, 1999), we have referred to two additional studies in this revised labeling (Amendment 027):

Creinin M. and Shulman T. "Effect of Nonsteroidal Anti-inflammatory Drugs on the Action of Misoprostol in a Regimen for Early Abortion." *Contraception,* 1997, 56:165-8 in the "Drug Interactions" subsection and;

Population Council

Van der Schoot, P. and Baumgarten, R. "Effects of treatment of male and female rats in infancy with mifepristone on reproductive function in adulthood." *J Reprod Fertil*, 1990, 90(1):255-66. in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection.

Copies of these articles are enclosed.

Thank you for your consideration of these changes. We look forward to your responses and working together to reach agreement upon the final labeling for this drug.

Sincerely,

Frederick H. Schmidt

for Sandra P. Arnold
Vice President, Corporate Affairs
Population Council

cc: [redacted] The Danco Group
Frederick H. Schmidt, Ph.D., Population Council
Patricia C. Vaughan, Esq., Population Council
[redacted]
[redacted] Food and Drug Administration

enclosures:
Appendix A: revised labeling
Appendix B: marked labeling
Appendix C: letter from USAN
Appendix D: misoprostol administration
Appendix E: articles referenced in cover letter
Appendix F: articles referenced in Appendix D

Population Council

October 21, 1999

The Danco Group

VIA FAX: 9-424-1952

Dear

On August 30, 1994, the Population Council received from Roussel Uclaf two (2) metallic containers, each containing mifepristone 200 mg tablets in polyethylene bag (bulk), Batch No. JMP 25524-109, Date of manufacture = July 1994, Expiration Date = July 1997. These tablets were stored at the Population Council; in an air-conditioned facility with normal controls of laboratory temperature and humidity.

On September 22, 1994 the above mifepristone tablets were repackaged into small bottles (amber plastic light resistant, bottle) with tablets per bottle. On September 26, 1994 these bottles were hand delivered to the for Stability Testing at room temperature and at an accelerated condition each for 0, 2, 6 and 12 months testing.

On November 7, 1997 and November 10, 1997 a total of mifepristone tablets, respectively, were repackaged from the metallic containers (stored at the Population Council under the same conditions described above) into small amber bottles. Then on November 11, 1997, these bottles (were sent to for Stability Testing at room temperature for extension of the July 1997 expiration date. performed stability tests on these tablets at 0, 6, 12, and 18 month intervals.

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

cc: S. Arnold
E. Johansson

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

NDA 20-687: Mifepristone Tablets, 200mg

SUMMARY OF APPROVABLE LETTER POINTS AND RELATED RESPONSES

	RESPONSE AMENDMENT #	DATE
1	033	August 18,1999
2	029 030	July 14,1999 July 22,1999
3	029	July 14,1999
4	029	July 14,1999
5	030	July 22,1999
6	030	July 22,1999
7	027	June 25,1999
8	033	August 18,1999
9	031	August 3, 1999
10	024	June 3, 1999
11	029	July 14,1999
12	033	August 18,1999
13	029	July 14,1999
14	029	July 14,1999
15	029	July 14,1999
16	030	July 22,1999
17	029	July 14,1999
18	030	July 22,1999
19	033	August 18,1999

Please see attached for description of each point raised in the Approvable Letter.

CHAPTER 9A.
VITAL STATISTICS

Effective date. — The act which added this chapter became effective May 21, 1992.

§ 22-9A-1. Definitions.

For the purposes of this chapter, the following words shall have the following meanings unless the context clearly indicates otherwise:

(1) DEAD BODY. A human body or parts of the human body from the condition of which it reasonably may be concluded that death occurred.

(2) FETAL DEATH. Death prior to the complete expulsion or extraction from the mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after the expulsion or extraction the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.

(3) FILE. The presentation of a vital record provided for in this chapter for registration by the Office of Vital Statistics.

(4) FINAL DISPOSITION. The burial, interment, cremation, removal from the state, or other authorized disposition of a dead body or fetus.

(5) INDUCED TERMINATION OF PREGNANCY. The purposeful interruption of an intrauterine pregnancy with the intention other than to produce a live-born infant and which does not result in a live birth. This definition excludes management of prolonged retention of products of conception following fetal death.

for the child for whom it is issued. After registration of the birth certificate in the new name of the adopted person, the State Registrar shall seal and file the report of adoption which shall not be subject to inspection except upon order of a court of competent jurisdiction or as provided by statute.

(2) If the child was born in a foreign country but was a citizen of the United States at the time of birth, the State Registrar shall not prepare a "CERTIFICATE OF FOREIGN BIRTH" and shall notify the adoptive parents of the procedures for obtaining a revised birth certificate for their child through the U.S. Department of State. (Acts 1992, No. 92-607, § 12.)

§ 22-9A-13. Reports of fetal death; reports of induced termination of pregnancy.

(a) A report of fetal death shall be filed with the Office of Vital Statistics, or as otherwise directed by the State Registrar, within five days after the occurrence is known if the fetus has advanced to, or beyond, the twentieth week of uterogestation.

(1) When a fetal death occurs in an institution, the person in charge of the institution or his or her designated representative shall prepare and file the report.

(2) When a fetal death occurs outside an institution, the physician in attendance shall prepare and file the report.

(3) When a fetal death occurs without medical attendance, the county medical examiner, the state medical examiner, or the coroner shall determine the cause of fetal death and shall prepare and file the report.

(4) When a fetal death occurs in a moving conveyance and the fetus is first removed from the conveyance in this state or when a dead fetus is found in this state and the place of fetal death is unknown, the fetal death shall be reported in this state. The county where the fetus was first removed from the conveyance or the dead fetus was found shall be considered the county of fetal death.

(b) A report of induced termination of pregnancy for each induced termination of pregnancy which occurs in this state shall be filed with the Office of Vital Statistics, or as otherwise directed by the State Registrar, no later than 10 days after the last day of the month during which the procedure was performed.

(1) When the induced termination of pregnancy is performed in an institution, the person in charge of the institution or his or her designated representative shall prepare and file the report.

(2) When the induced termination of pregnancy is performed outside an institution, the physician in attendance shall prepare and file the report.

(3) Reports of induced termination of pregnancy shall not contain the name or the address of the patient whose pregnancy was terminated, nor shall the report contain any other information identifying the patient.

(4) Individual induced termination of pregnancy reports shall be maintained in strict confidence by the Office of Vital Statistics, shall not be

available for public inspection, shall not be available in court for any purpose, and shall not be subject to discovery in any civil action except as provided in subdivision (b)(5) of this section.

(5) The Office of Vital Statistics shall periodically make available aggregate data about the induced terminations of pregnancy performed in this state, but the Office of Vital Statistics shall not release the names of individual physicians or other staff members employed by institutions performing induced terminations of pregnancy. The Office of Vital Statistics shall not release the number of procedures performed by any particular institution or physician, except at the request of the board or its attorney pursuant to an investigation of civil or criminal legal action related to licensure or the need for licensure of health facilities or similar investigation or legal action for failure to file reports required by this section.

(6) The State Registrar may authorize the use of other aggregate statistical data for official government use.

(c) The reports required under this section are statistical reports only and are not to be incorporated into the official records of the Office of Vital Statistics. Certified copies of these records shall not be issued by the Office of Vital Statistics. Except when copies of reports must be maintained pursuant to subdivision (b)(5) of this section, the State Registrar shall dispose of all individual reports received as soon as practicable after data from the forms is transferred to the database of the Center for Health Statistics, or after the board or its attorney declares there is no further need for the forms pursuant to subdivision (b)(5) of this section. Such disposal shall follow procedures of the State Records Commission.

(d) Subsection (c) shall also apply to all records of fetal death and induced termination of pregnancy filed in the Office of Vital Statistics prior to adoption of this chapter. (Acts 1992, No. 92-607, § 13.)

§ 22-9A-14. Death registration.

(a) A certificate of death for each death which occurs in this state shall be filed with the Office of Vital Statistics, or as otherwise directed by the State Registrar, within five days of the death and shall be registered if it has been completed and filed in accordance with this section.

(1) If the place of death is not known, but the dead body is found in this state, the certificate of death shall be completed and filed in accordance with this section. The county where the body is found shall be shown on the certificate as the county of death. If the date of death is unknown, the date the dead body was found shall be shown on the certificate as the date of death.

(2) When death occurs in a moving conveyance in the United States and the body is first removed from the conveyance in this state, the death shall be registered in this state and the county where it is first removed shall be considered as the county of death. When a death occurs on a moving conveyance while in international waters or air space or in a foreign

FROM: FAX 01-11-00 04:12P P.01

Exhibit D

Dear

s is requesting to store non-controlled product in the caged staging area that is in front of our vault. Today no controlled drugs are stored in this limited access area. This request is to store limited quantities , of this non-controlled product. This product is controlled by serial number and requires a limited secure access storage area. This product requires special steps to be in place to insure that each package is accountable and secure from the manufacture to the patient.

The product is called Mifeprex (mifepristone). It is an oral antiprogestin agent, which blocks the action of the hormone progesterone and thus requires tracking of the product to the patient level.

Please consider this request. If there are any questions or if you need further information, my number Thank you in advance for help.

Regards,

/S/

Director of Operations

Exhibit D

US Department of Justice
Drug Enforcement Administration
600 Arch Street, Room 10224
Philadelphia, Pennsylvania 19106

Dear

. is requesting to store non-controlled product in the caged staging area that is in front of our vault. Today no controlled drugs are stored in this limited access area. This request is to store limited quantities (two pallets) of this non-controlled product. This product is controlled by serial number and requires a limited secure access storage area. This product requires special steps to be in place to insure that each package is accountable and secure from the manufacture to the patient.

The product is called Mifeprex (mifepristone). It is an oral antiprogestin agent, which blocks the action of the hormone progesterone and thus requires tracking of the product to the patient level. This is not a short-term request. The business relationship is contracted

Please consider this request. If there are any questions or if you need further information, my number is Thank you in advance for help.

Regards,

Danco Inc.

May 16, 2000

Dear ____

Enclosed, please find the information as per your request on the purification procedure and spectral data on Mifepristone (internal lot #CQ-00-08 which is same as lot# MIFE-9602-01).

If you have any further question, please call me at _____

Sincerely,

/S/

APPEARS THIS WAY
ON ORIGINAL

memorandum

Danco Investors Group, L.P.
March 31, 1999

- *FDA Submission (CMC Section)*: This document is currently under preparation following our guidance, and a final draft is expected to be available for our review April 15, 1999.

Taking the above synopsis under consideration, we expect to audit the
one more time (*early June*) and it is our opinion that the company should be ready for pre-approval inspection in July of this year.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
3	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE	SERUM HCG
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___°C	___ ___ ___ ___ ___ ___ IU/L

HCT	HgB
___ ___ %	___ ___ g/dL

(circle one)

Did the patient report any symptoms since Visit 2?
No
Yes (record on page 12)

Did the patient use any concomitant medications since Visit 2?
No
Yes (record on page 13)

Review patient diary for adverse events and medication use.

ABORTION STATUS

(circle one)

Does the patient believe that expulsion occurred after Visit 2 and prior to Visit 3?
No (go to page 10)
Unsure (complete below)
Yes (complete below)

Date of expulsion: ___/___/___ M D Y

Time of expulsion: ___ ___:___ ___ (24 hour clock)

Dear :

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

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

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

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

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

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

_____ _____

Print Name Signature

BNDD#:_____ Medical License #:_____

ROUSSEL UCLAF

Direction du Développement Préclinique

RU 38486

STUDY OF THE DEVELOPMENT AND FERTILITY OF YOUNG RATS TREATED SUBCUTANEOUSLY WITH A SINGLE INJECTION ON DAY 1 AFTER BIRTH

(1, 10, 100 mg/kg)

[redacted]

Reference: 92/4183/TX

Date: October 1994

Number of pages: 120

SYNOPSIS

Study no:	92/4183/TX
Compound:	RU 38486
Batch no. (Control number):	8 V 1238 B
Activity:	Antiprogesterone
Species, race:	Rat, Sprague-Dawley OFA, S.P.F. Caw
Number of animals:	The offspring of 14 to 15 litters, i.e. about 200 young per group.
Treatment	
Doses:	0, 1, 10 and 100 mg/kg/day.
Route:	Subcutaneous
Period:	Day 1 after birth
Number of administrations:	One only, in a volume of 6 ml/kg
Formulation:	In solution in maize oil

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

F

January 22, 1993

Edouard Sakiz, M.D.
President, Roussel-Uclaf
102 route de Noisy
F-93230 Romainville

Dear Dr. Sakiz:

This letter is pursuant to my letter to you of December 15, 1992, and confirms my meeting with you and Dr. Andre Ulmann to take place as soon as possible. I understand that sometime during the first 3 days of February may be possible.

The purpose of the meeting is to discuss possible therapeutic uses of anti-progestational drugs and, in particular, our interest in receiving a New Drug Application for approval of mifepristone for interruption of early pregnancy. Several of my colleagues will also attend the meeting.

I am pleased that you and Dr. Ulmann are able to respond to my invitation to discuss these important issues. My office will work with yours in establishing when we shall meet.

Sincerely yours,

David A. Kessler, M.D.
Commissioner of Food and Drugs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

G

February 3, 1993

Professor Wolfgang Hilger
President of the Board
Hoechst AG
D-6230 Frankfurt-am-Main 80
GERMANY

Dear Professor Hilger:

The Food and Drug Administration contacted Dr. Edouard Sakiz of Roussel-Uclaf in December 1992 to discuss the availability of mifepristone in the United States for research and marketing.

The purpose of this letter is to inform you directly of our interest in this important matter. The Food and Drug Administration wants the opportunity to review a New Drug Application for RU-486 for termination of early pregnancy. To that end, we think that Roussel-Uclaf should submit an application as soon as possible. If Roussel-Uclaf thinks that additional research on RU-486 is required, Dr. Sakiz should advise us as to what research he thinks is necessary and provide us with a time frame for conducting such research. We would appreciate it if you would expedite progress in this regard.

At our February 24, 1993 meeting with Dr. Sakiz we plan to discuss the status of knowledge concerning the safety and efficacy of the drug, the readiness for a New Drug Application for this indication, the suitability of a treatment IND as an interim undertaking, and the identity of the applicant.

We would appreciate hearing your views on this matter. I can be reached at (301) 443-2410 and my mailing address is: Room 14-71 Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely yours,

David A. Kessler, M.D.
Commissioner of Food and Drugs

cc: Dr. Edouard Sakiz

3/12/93 The Secretary wrote to the president of Hoechst, the parent company of Roussel Uclaf, to urge him to eliminate corporate barriers to the introduction of RU-486 into the United States.

[redacted]

[redacted] APPEARS THIS WAY
[redacted] ON ORIGINAL

[redacted]

FYI
/ has no record of stated

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, March 18, 1993

Mrs. Donna E. Shalala
Secretary of the Department of Health
& Human Services
H.H.H. Building - Room 615 F
Washington, D.C. 20201
U.S.A.

Dear Mrs. Shalala,

It was very thoughtful of you to send me a copy of your March 12 letter to Professor Wolfgang Hilger, for which I thank you very much.

The Roussel Uclaf Group and I appreciate your commitment to the expansion of safe and effective healthcare choices for American women for the termination of unwanted pregnancy. The comments contained in your letter also reflect President Clinton's determination to keep the promises he made throughout his campaign.

The message delivered to Professor Hilger will greatly contribute to progress further in order to sort out the complexities of the issues involved in any decision to make the drug available in the United States.

The meeting held last month with Dr. Kessler is already proving very rewarding as new steps are going to be considered with the help of Margaret Catley-Carlson, the President of the Population Council, who has also assured us of her support wi regard to getting clinical trials started in the United States.

In view of the clinical studies and the training program which are to be undertaken because French and US regulations concerning early termination of pregnancy are not the same, it will still take some time before RU 486 is made available to American women.

I will be pleased to keep you informed of any further development.

Yours sincerely,

T54997

9301600

TRACER

35, Boulevard des Invalides 75007 Paris
Tél. + 33 (1) 40 62 44 28 Fax. + 33 (1) 40 62 44 90 Tlx. GRUPA 200 675 F

PROF. DR. WOLFGANG HILGER
VORSITZENDER DES VORSTANDS
HOECHST AKTIENGESELLSCHAFT

6230 FRANKFURT AM MAIN 80
POSTFACH 80 03 20
TELEFON (0 69) 3 05-7 8 39

March 23, 1993

The Secretary of Health and Human Services
Mrs. Donna E. Shalala
Washington, D.C. 30201

U.S.A.

Dear Mrs. Shalala:

Many thanks for your letter of March 12, 1993, which I have received by fax.

I would like to describe the present situation in the USA as follows:

On the request of the Food and Drugs Administration, a meeting with Dr. Edouard Sakiz, President of Roussel Uclaf has taken place to discuss relevant question on the drug RU 486.

In their wide-ranging discussions both sides recognized the complexities of the issue, involved in any decision to make the drug available in the United States.

The FDA has clearly pointed out that you are very much willing to see RU 486 made available in the USA. However, the FDA accepts that Roussel Uclaf has no intention to approach the FDA to obtain marketing licence for the drug. The FDA has undertaken to approach third parties who are competant and might be interested to sponsor clinical studies and to market the drug in the USA. Because the drug is currently available only under very restricted distribution (France, the United Kingdom and Sweden) it will become necessary that the FDA will issue new regulation to control the use and distribution.

Both sides will continue their consultations to clarify the many open questions on the issue. At a later stage a common decision on how to proceed in the USA will be taken.

Yours sincerely,

Wolfgang Hilger.

93-1820

M

PROF. DR. WOLFGANG HILGER
VORSITZENDER DES VORSTANDES
HOECHST AKTIENGESELLSCHAFT

6230 FRANKFURT AM MAIN 80
POSTFACH 80 03
TELEFON (0 69) 30-01

Dr. David Kessler
Commissioner of the
Food and Drug Administration
5600 Fishers Lane, HF-40
Rockville, Maryland 20857
U.S.A.

April 15, 1993

Fax: 001-301-443-1863

Dear Dr. Kessler,

Thank you for your letter of April 14 concerning the meeting you propose on the Roussel Uclaf compound RU 486.

We are both aware that the development of RU 486 in the field of abortion has confronted us with an extremely complex social issue which is almost impossible to resolve in a way that would be acceptable to all concerned.

In spite of our position to not be involved in the marketing or production of RU 486 for the American market, we are making a considerable effort to respect your intention to make the compound available to the medical profession in the United States.

I am aware that substantial progress has been made since your last meeting with Dr. Sakiz on February 24 in Washington D.C.

If the FDA considers a clinical trial to be necessary, you know that it can be carried out by the Population Council, with whom Roussel Uclaf has a long-standing agreement on this compound.

Concerning the eventual distribution in the United States, this can only be done through third parties, as we have always indicated and as I have reiterated in my press conference on March 23.

The question of production can be resolved as indicated in the Roussel Uclaf agreement with the Population Council, which permits a transfer of their production technology to a third party.

I know that Dr. Sakiz will be meeting with you on April 20 to determine the next steps to be taken to make RU 486 available in the United States. He is the most knowledgable individual on this issue within the Hoechst organization and is fully aware of all the problems concerning RU 486. We are entirely confident that he is the best representative we could send for the meeting you have proposed. I believe that sending another representative of Hoechst would serve no useful purpose.

Be assured that I am following this matter very closely and am confident that a satisfactory solution for all parties can be found.

Sincerely yours,

W. Hilger.

93-1744

Could you please inform the FDA's [redacted] as soon as possible that this information has been filed. The [redacted] had recently indicated that they required this action before the drug substance could be shipped by Danco to the site.

Please let me know if you require any additional information.

Sincerely,

/S/ /S/

President and
Chief Executive Officer

/dns
Enclosure

CC: [redacted]
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council
[redacted]
[redacted] - FDA

[redacted] THIS WAY
[redacted]GINAL

ORIGINAL

The Danco Group

[ ]

ORIG AMENDMENT

May 20, 1999

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 023 - Site Details of Drug Product Manufacturer

Dear ———

We are providing site details for Danco's Drug Product Manufacturer for mifepristone:.

Site and Mailing Address: [ ]

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ DATE

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

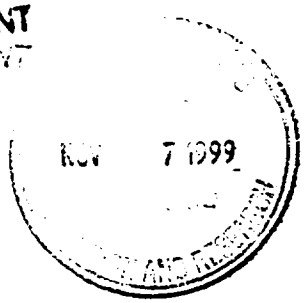
The Danco Group

ORIGINAL

November 16, 1999

ORIG AMENDMENT

BC



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

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

- Amendment 036 - Supplemental Information to Drug Substance and Drug Product Chemistry, Manufacturing and Controls (CMC) Submissions

Dear ———

We are responding to your request for additional detail regarding the Drug Substance and Drug Product CMC submissions.

1. Certificate of Analysis of Roussel Mifepristone Lot 4V 1014 BJ.

   We are enclosing the Roussel Certificate of analysis for this lot (Attachment 1) . This is the lot that has been referred to in the Drug Substance CMC, submitted as Amendments # 025 and #028.

   Following your request, a reanalysis of a sample from this lot is currently underway. We will report those results as soon as they become available The method of analysis used is the same —— method that we have used previously both in China and at ——— and that is currently being re-validated ———

2. Certificates of Analysis for ———

   We are enclosing the certificates of analysis for the ——— batches referred to in our Drug Substance CMC, submitted as Amendment #028 (Attachment 2).

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

3. Originals for the ——— in the Drug Substance CMC.

   Copies of this data were originally provided in our Drug Substance CMC, submitted as Amendment #025. The source laboratory of these data, ———, has reprinted their original data which are enclosed (Attachment 3).

4. Excipient Suppliers' Certificates of Analysis for Drug Product Batch # 99005.

   We are enclosing suppliers' Certificates of Analysis for those excipients that were utilized in the manufacture of Drug Product (Attachment 4). These data were included in the original Drug Product CMC, submitted as Amendment #032 and are provided here again for ease of reference.

5. Environment Assessment for Drug Product and Drug Substance.

   Since the expected introduction concentration (EIC) calculations for the Drug Product produced at — result in a value of ——— which is less than 1.0 ppb, the Tier 0 Criteria are met. (Attachment 5). We therefore request Categorical Exclusion from filing a formal Environment Assessment Section for the Drug Product manufactured at —

   We are awaiting the appropriate Environmental Compliance certificates for Drug Substance from Shanghai HuaLian Pharmaceutical Corporation. These are expected shortly and we will provide you with the information as soon as possible.

In addition, we are preparing the Methods Validation Packages for Drug Substance and Drug Product. This information will be provided together with samples of Drug Substance and Drug Product as well as a sample of the primary impurity in mifepristone, ———

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

Sincerely,

/S/

———

President and
Chief Executive Officer

/dns
Enclosures

REVIEW COMPLETED

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

———

——— - FDA

Danco Laboratories, LLC

640 Fifth Avenue, 13th Floor, New York, New York 10019
Tel: (212) 424-1950 Facsimile: (212) 424-1952

VIA FACSIMILE: [redacted]

September 25, 2000

[redacted]
Center for Drug Evaluation
and Research
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Dear [redacted]

Pursuant to your discussions this morning with [redacted] I wish to advise that Danco Laboratories, LLC:

- Has never heard of [redacted]
- Has not used [redacted] for any purpose in connection with any product of Danco
- Has no plans to utilize the services of [redacted] in the future

Separately, we expect to import drug substance approximately [redacted] times per year.

Sincerely,

[redacted] /S/

'PEARS THIS WAY
ON ORIGINAL

/dns

cc: [redacted]

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 [redacted]

Nov. 21, 1995

Please search your paper & electronic files and notes for the requested documents and return to ——— by Nov. 29. If you find nothing, please send a message to that effect.

Thank you,

———.

APPEARS THIS WAY
ON ORIGINAL

CONGRESSIONAL REQUEST

CENTER FOR DRUG EVALUATION & RESEARCH
EXECUTIVE SECRETARIAT STAFF
CONTROL FORM

FROM: **REPRESENTATIVE TOM A. COBURN, M.D.***

TO : Dr. David A. Kessler

SUBJ: DOCUMENT REQUEST: RU-486

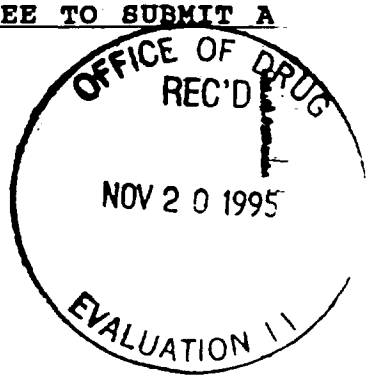
***PLEASE TREAT AS A CHAIRMAN DOCUMENT REQUEST AND PROVIDE ALL DOCUMENTS. REPRESENTATIVE COBURN WILL MOST LIKELY REQUEST THE CHAIRMAN OF THE HEALTH AND ENVIRONMENT SUBCOMMITTEE TO SUBMIT A LETTER IN ORDER TO OBTAIN ALL DOCUMENTS.**

DATE OF DOCUMENT: 11/10/95**

DATE REFERRED : 11/20/95

DUE DATE : **11/30/95**

CONTROL NUMBER : HFD-8-11-14C



**Not received in CDER until 11/20/95!

ROUTING SECTION

OFFICE	DATE REFERRED		
HFD-1	11/20/95	cc: HFD-6/ ———	
HFD-2	11/20/95	HFD-6/ ———	
HFD-3	11/20/95		
HFD-4	11/20/95		
HFD-5	11/20/95		#92
HFD-101/HFD-120	11/20/95	to HFD-510 11/20/95	due 11/30/95
HFD-101/HFD-150	11/20/95	— 11/20/95	due 11/30/95 #92
HFD-300	11/20/95		
HFD-102/~~HFD~~-510	11/20/95	Rec'd 11/21/95	
HFD-210	11/20/95		

INSTRUCTIONS: DOCUMENT REQUEST.

REMARKS: Documents thru HFD-1/ ——— WOC 2, Room ———

HAND CARRY, PLEASE.

COMMENTS:

+/-

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA
COMMITTEE ON COMMERCE
SUBCOMMITTEES
TELECOMMUNICATIONS AND FINANCE
HEALTH AND ENVIRONMENT
ENERGY AND POWER

Congress of the United States
House of Representatives
Washington, DC 20515–3602

511 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701
(202) 225-3038 (FAX)

215 STATE STREET, SUITE 815
MUSKOGEE, OK 74401
(918) 687-2533
(918) 682-3503 (FAX)

November 10, 1995

Dr. David A. Kessler
Commissioner
U.S. Food and Drug Administration
Room 14-71
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

As a member of the House Commerce Committee's Subcommittee on Health and the Environment, I write to request copies of documents in the possession of the Food and Drug Administration, including any of its advisory committees, relating to the drug known as RU 486 (mifepristone), developed by the company Roussel Uclaf SA.

I understand that the Population Council has an active investigational new drug application (IND) to use RU 486 for abortion. Several reports have appeared which indicate extensive communications between representatives of the Clinton administration and private companies and organizations, including the Population Council, concerning the future availability of RU 486 for use as an abortion pill in the United States. These reports, together with issues raised in a Citizens' Petition on RU 486 recently submitted to the FDA, have generated serious concern for public safety and the integrity of the drug approval process. Consequently, I am requesting that you provide the following information:

1) Any and all written or recorded communications, including electronic or telephonic communications, to or from the persons listed below relating to RU 486 from January 1, 1992 up to the present (i.e., up until the time the document search is conducted).

When used in the above request, the word "communication" includes, but is not limited to: correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all communications which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., communications relating to the acceptability of foreign data in the drug approval process).

For each such communication, please indicate the date of the communication, the names and the professional or organizational affiliations of all persons involved or present, the locations of meetings, and the offices within the FDA from which the communications were obtained. Also, please indicate which communications, if any, are confidential and may not be disclosed to the public.

This request includes all communications sent to or by the following persons from January 1, 1992 up to the present:

President Clinton, Mrs. Clinton, and White House staff
Other administration officials or personnel, including yourself, your assistant [redacted] and [redacted] of the Endocrine Drugs Division of the FDA
Edouard Sakiz, Dr. Andre Ulmann, and other officers, employees, or representatives of Roussel Uclaf
Margaret Catley-Carlson, Dr. Wayne Bardin, and other officers, employees, and representatives of the Population Council
David A. Grimes, M.D.
Daniel R. Mishell, M.D.
Suzanne Poppema, M.D.
Officers, employees and representatives of the following companies and organizations:
Hoechst AG of Frankfurt, Germany
Hoechst Celanese Corporation of Somerville, New Jersey
Hoechst-Roussel Pharmaceuticals of Somerville, New Jersey
Rhone-Poulenc of Paris
Schering AG of Berlin, Germany
G.D. Searle Company of Skokie, Illinois
Upjohn Company of Kalamazoo, Michigan
Gynopharma, Inc. of Somerville, New Jersey
Cabot Medical Corporation of Langhorne, Pennsylvania
Aurora Medical Services of Seattle, Washington
Fund for the Feminist Majority
Planned Parenthood Federation of America
Reproductive Health Technologies Project
National Abortion Federation
National Abortion and Reproductive Rights Action League (formerly the National Abortion Rights Action League)
Oregon Science Health University of Portland, Oregon
Center for Reproductive Law and Policy
National Organization for Women
Women's Issues Network

2) Any and all documents relating to the implementation of President Clinton's January 22, 1993, memorandum for the Secretary of Health and Human Services regarding the importation of RU 486.

In this memorandum, the President asked the Secretary to take the following three actions:

a) "promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption;"

b) "immediately take steps to rescind Import Alert 66-47" if the "FDA concludes that RU-486 meets the criteria for the personal use importation exemption;" and

c) "promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 and other antiprogestins."

When used in the above request, the word "document" includes, but is not limited to: internal and external documents of the Food and Drug Administration, documents prepared by persons or offices outside the FDA (including documents prepared by non-governmental persons, organizations, or companies), correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all documents which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., criteria for the acceptance of foreign data, etc.). For each such document, please indicate the date of the document, the author or authors of the document, the persons to whom it was given or sent, and the offices within the Department from which the documents were obtained. Please separate the documents in this second request into three categories based on which of the three actions requested by the President the documents address. Again, please indicate which communications, if any, are confidential and may not be disclosed to the public.

Thank you for your attention to this inquiry. A similar request for documents has been submitted to Secretary Shalala. I look forward to receiving the information by December 1, 1995. If you foresee any difficulty in fulfilling this request by that date, please notify me immediately. Roland Foster on my staff will be available to work with you if you have any questions.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

ORIGINAL
ORIG AMENDMENT

The Danco Group

August 13, 1999

[redacted]

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

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 032 - Chemistry, Manufacturing and Controls (CMC) Section II for Drug Product

Dear [redacted]

This Amendment 032 is the complete CMC section for our Drug Product.

As agreed during our April 9, 1999 meeting with the FDA, we are filing the CMC section with one-month room temperature stability data and one month accelerated stability data. We will provide three months room temperature and three months accelerated stability data in October. We request that the FDA initiate review of this CMC submission as soon as possible.

Under separate cover a copy of this CMC section has been sent to the attention of [redacted], at [redacted] U.S. Food and Drug Administration District Office.

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

/S/

Sincerely,

/S/

[redacted]
President and
Chief Executive Officer

APPEARS THIS WAY
ON ORIGINAL

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

/dns
Enclosure

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

[redacted] - FDA
[redacted] - FDA- [redacted] FDA Office

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

NEW CORRESP

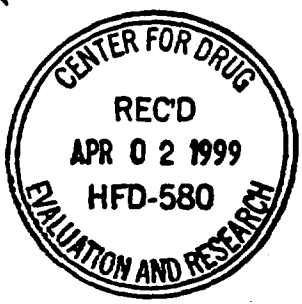
NC [illegible]

The Danco Group

March 31, 1999

/S/ 4/6/99 noted 4/6/99 /S/

hold w/ (S) 4/5/99



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

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

- Amendment 020 – Confirmation and Documentation for meeting April 9, 1999 10:00am – 11:30am

Dear ———

This letter confirms our arrangements to attend the April 9, 1999 (10:00am to 11:30am) meeting you have scheduled following our March 30, 1999 telephone call with ——— We appreciate the availability of the various Division staff for this meeting.

To facilitate discussion we are enclosing a brief timeline for our Drug Substance and Drug Product manufacturing activities together with targets for submissions to the FDA. (Exhibit 1)

AGENDA

I. Population Council/Danco update on Drug Substance Supply arrangements

A. Status (Exhibit 2)

B. Given the limited visits by the FDA to the country of manufacture, will the FDA be willing to plan ahead and target the Pre-Approval Inspection (PAI) for this site in the June/July period, following an end April/early May Drug Substance CMC submission with three months accelerated stability? (Drug Product CMC with one month accelerated stability will be filed in early June.)

II. Population Council/Danco Update on Drug Substance and Drug Product testing arrangements in the United States.

A. Facility

REVIEWS COMPLETED

CSO ACTION:

☐ LE[illegible] ☑ N.A.[illegible] ☐ MEMO

/S/ 4/6/99

Printed by Jane Axelrad

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 26-Sep-2000 02:19pm
From: [redacted]

Dept:
Tel No:

TO: [redacted]
TO: [redacted]

Subject: FW: Registration/Listing Requested Info

According to this information I received in June, the chinese firm has a number of products listed.

[redacted]

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution, or copying is strictly prohibited. If you think you have received this email in error, please e-mail the sender immediately at [redacted]

-----Original Message-----
From: [redacted]
[mailt [redacted]
Sent: Friday, June 30, 2000 1:30 PM
To: [redacted]
Subject: Registration/Listing Requested Info
Sensitivity: Confidential

Here are the registration and listing info - hope it helps!

[redacted] Labeling code for Co - other products 64163=1 64877=1 mfr

The firms are:

Danko [redacted] - may be a private labeler - is drug listing required?

No record of this firm in data base.

Shanghai Hualian Pharmaceutical
201419
Shanghai, China
(Note: We believe this firm has previously registered and listed...)

There is a firm "Shanghai Hualian Pharmaceutical Co, Ltd." registered in the data base (LC 064163; CFN FCCH442). With a Compliance Address: 370 Jiang Wan Rd West, Shangai 200083 China. They have multiple listings:

201237 064163 0001 MEDROXYPROGESTERONE ACETATE

201238 064163 0002 ESTRIOL
178166 064163 0211 DEXAMETHASONE SODIUM PHOSPHATE
178167 064163 0212 ESTRIOL
181723 064163 2001 SPIRONOLACTONE MICRO USP 23
178925 064163 2250 BECLOMETHASONE DIPROPIONATE
178926 064163 2820 BETAMETHASONE SODIUM PHOSPHATE

Let me know if you need/want more info on any of the above.

Printed by [redacted]

Electronic Mail Message

Date: 30-Jun-2000 01:29pm
From: [redacted]
Dept: HFD-324 MPN1 265
Tel No: [redacted]

Subject: Registration/Listing Requested Info

Here are the registration and listing info - hope it helps!

The firms are:

Danko - [redacted] - may be a private labeler - is drug listing required?

No record of this firm in data base.

Shanghai Hualian Pharmaceutical
201419
Shanghai, China
(Note: We believe this firm has previously registered and listed...)

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178926 064163 2820 BETAMETHASONE SODIUM PHOSPHATE

[redacted]

Let me know if you need/want more info on any of the above.

Printed by

Electronic Mail Message

Date: 08-Jun-2000 04:28pm
From:

Dept:
Tel No:

TO:

Subject: Benten v. Kessler 1995 brief

Attached is the 1995 brief.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

FRANK W. HUNGER
Assistant Attorney General
Civil Division

DRAKE CUTINI
Office of Consumer Litigation
U.S. Department of Justice
P.O. Box 386
Washington, D.C. 20044
(202) 307-0044

ZACHARY W. CARTER
United States Attorney

CHARLES KLEINBERG
Assistant United States Attorney

Attorneys for Defendants

LEONA BENTEN, Plaintiff, v. DAVID KESSLER, et al., Defendants.	Civil No. 92-3161 **MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT**

INTRODUCTION

As outlined in defendants' brief in support of their motion to dismiss, plaintiff has requested this Court to enter a judgment that would prevent the United States Food and Drug Administration (FDA) from enforcing the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and to order the FDA and the Customs Service to allow an unapproved drug to be illegally imported into the United States.

In examining plaintiff's attempt, it is important to note that there is no "import ban" on the importation of RU486 (mifepristone), as plaintiff has characterized the import alert.

RU486 is permitted into the country when imported as part of Investigational New Drug (IND) studies, and it is being imported at the present time for studies for abortifacient and non-abortifacient uses. FDA has in no way interfered with the importation of RU486 when used as part of a careful, controlled study pursuant to an IND, and has publicly indicated support for such studies. Such INDs are part of the comprehensive, thorough, and detailed statutory process that Congress has required to be utilized in order for a drug to be legally marketed in this country. The culmination of this process is the submission of a New Drug Application (NDA) by the party seeking to manufacture or distribute a drug, and the FDA's analysis of this application. A drug can only be approved under this process if FDA concludes that it is "safe and effective" for its intended use after review of the voluminous NDA.

It is undisputed that RU486 has not gone through this process, and is not approved for use in this country outside of IND trials. Although FDA has done nothing to hamper the drug approval process, plaintiff seeks to evade this process altogether by having this Court conclude that RU486 is safe and effective for use as an abortifacient, and should be permitted into the country without restriction for that use. In other words, plaintiff wants this Court to take over the functions of the FDA. As discussed below, the scientifically-based drugapproval process is intricate and thorough and requires a significant amount of scientific knowledge and expertise, which is one of the main reasons that Congress has entrusted the task to FDA.

Congress has also entrusted FDA with the authority and discretion to prevent the importation of drugs that are not approved in this country. It is undisputed that RU486 is not approved; thus, FDA has authority and discretion to preclude the importation of this drug. The agency does not need to engage in rule-making procedures to enforce the law. As defendants demonstrated in their motion to dismiss, this case should be dismissed as moot because it is unlikely that plaintiff will again attempt to bring this drug into the country. The case should also be dismissed because the challenged action is committed to agency discretion and because plaintiff has failed to exhaust her administrative remedies.

However, if the case is not dismissed for those reasons, judgment should be granted in favor of the defendants because the challenged import alert is not a rule for which notice and comment were necessary, because the import alert is reasonable and not arbitrary or capricious, and because it does not violate the Constitution. These issues are discussed in further detail below. Also, this case is now moot for a second reason notdiscussed in the defendants' motion to dismiss, and that reason is discussed below.

ARGUMENT

As defendants discussed in their initial memorandum, it is well-established that "federal courts are without power to decide questions that cannot affect the rights of litigants in the case before them." North Carolina v. Rice, 404 U.S. 244, 246 (1971). "To invoke the jurisdiction of a federal court, a litigant must have suffered, or be threatened with, an actual injury traceable to the defendant and likely to be redressed by a favorable judicial decision." Lewis v. Continental Bank Corp., 494 U.S. 472, 477 (1990).

The "case-or-controversy requirement subsists through all stages of federal judicial proceedings, trial and appellate." Id. at 477. See also New York City Employees' Retirement System v. Dole Food Co., 969 F.2d 1430 (2d Cir. 1992); Deeper Life Christian Fellowship, Inc. v. Sobol, 948 F.2d 79, 81 (2d Cir. 1991); Christopher P. v. Marcus, 915 F.2d 794, 802 (2d Cir. 1990), cert. denied 498 U.S. 1123 (1991).

Even though some cases are not moot because the issues are "capable of repetition, yet evading review," this doctrine is applicable only in "exceptional situations." See Lewis, supra, 494 U.S. at 481; Deeper Life, supra, 948 F.2d at 82. The SupremeCourt has stated that, in order to meet this limited exception, the challenged action must be too short in duration to be fully litigated prior to its cessation, and there must be a "reasonable expectation" or "demonstrated probability" that the same controversy will recur involving the same parties. Murphy v. Hunt, 455 U.S. 478, 482 (1982). A "mere physical or theoretical possibility" of repetition is insufficient. Id. See also Lewis, supra, 494 U.S. at 481; Weinstein v.Bradford, 423 U.S. 147, 149 (1975); Deeper life, supra, 948 F.2d at 82; Direct Marketing Association v. U.S. Postal Service, 721 F.2d 55, 58-59 (2d Cir. 1983) ("unusual circumstances" make case "not likely to recur."); Trane Co. v. O'Connor Securities, 718 F.2d 26, 27 (2d Cir. 1983) (while recurrence was "abstractly ... conceivable," it was not likely).

Although this Court has stated that the fact that plaintiff Benten has terminated her pregnancy does not moot this case, Memorandum and Order on Motion to Intervene at 3, Sept. 30, 1992, additional factors render plaintiff's complaint moot and not capable of repetition. As discussed in defendants' memorandum in support of their motion to dismiss, it is not likely that plaintiff will be able to attempt to bring RU486 into the country again to challenge FDA's import alert, and the case is moot for that reason.

An additional reason that this case is now moot is that RU486 is presently available in this country for investigational use as an abortifacient, and there is nothing to suggest thatplaintiff could not now obtain this drug legally in the United States for that purpose. As shown in Attachment A hereto, the Population Council has stated that it is presently clinical trials of RU486 at various clinics around the country. As that

News Release makes clear, the manufacturer of RU486, Roussel Uclaf, donated the U.S. rights to the drug to the Population Council, without renumeration. Attachment A at 2. The Population Council plans to submit a New Drug Application to the FDA and hopes to gain FDA approval by 1996. Id. at 2, 6. In an earlier News Release, the Population Council noted that these clinical trials required that it amend its current IND. Attachment B.

This drug would be available to plaintiff as a participant in the clinical trial under the IND. The record reflects that plaintiff has associations with people connected to the ongoing clinical trial. One of plaintiff's declarants for her 1992 complaint, Dr. Wayne C. Bardin, is Vice President of the Population Council and, apparently, submitted the IND that is currently underway on their behalf. See Declaration of Wayne C. Bardin at 1-3; Attachment A at 1. Another of plaintiff's declarants, Dr. David Grimes, is stated to have "[c]onducted clinical trials with mifepristone," and has the "most experience with [the] drug in U.S."). See Attachment A listing of "Mifepristone Expert Resources Group." Moreover, plaintiff'sphysician, Dr. Louise Tyrer, stated in her Declaration that plaintiff Benten is an appropriate candidate for RU486, and that Dr. Tyrer has met with Dr. Grimes and with the person who developed RU486. See Tyrer Declaration, exhibit B to plaintiffs' memorandum in support of their motion for preliminary relief.

There is no evidence to indicate that FDA has ever restricted in any way the importation of RU486 for legitimate research pursuant to INDs. See RU486 Hearings, Testimony of Ronald Chesemore at 35, 36, 43, 46, statement of Dr. Sobel at 40, 50-51; statement of Ms. Barnes at 42, 48. Also, the Secretary of HHS and the Commissioner of the FDA have encouraged the submission of an NDA for RU486. FDA has written to the manufacturer of RU486, Roussel Uclaf, and both HHS and FDA have met with Roussel Uclaf and Population Council representatives. See Statement By David A. Kessler, M.D., Commissioner of FDA Before the Subcommittee on Regulation, Business Opportunities, and Technology, Committee on Small Business, U.S. House of Representatives, May 16, 1994, Attachment C hereto. FDA has stated its willingness to work with the Population Council "to make certain that their clinical trials are well-designed and carefully conducted." Id. at 3.

Thus, contrary to plaintiff's argument, Memorandum in Support of Plaintiffs' Motion for Summary Judgment (Pl. Mem.) at 2, this drug is now available to plaintiff through clinical trials and her complaint is, therefore, moot. For this reason, plaintiff's complaint should be dismissed.

II. IMPORT ALERT 66-47 IS NOT A RULE REQUIRING PUBLICATION

Plaintiff's characterization of the FDA's internal guidance

concerning its enforcement policy as an Administrative Procedure Act (APA) "rule" subject to notice and comment must be rejected. In fact, the Supreme Court stated that plaintiff had "failed to demonstrate a substantial likelihood of success" on this very issue. Benten v. Kessler, 112 S.Ct. 2929 (1992) (per curiam). Import alert 66-47 is simply not a rule, but agency guidance regarding its enforcement policy, and it is intended solely as guidance to FDA employees. Further, plaintiff's attempt to strike down this alleged "rule" so that she can take advantage of the personal use policy is unavailing. Neither of these policies creates rights or obligations nor do they give plaintiff any "right" to import RU486.

The APA notice and comment requirements do not apply to "interpretative rules, general statements of policy or rules of agency organization, practice or procedure." 5 U.S.C. § 553(b). The exceptions "accommodate situations where the policies promoted by public participation in rulemaking are outweighed by the countervailing considerations of effectiveness, efficiency, expedition and reduction in expense." Guardian Federal Savings and Loan Ass'n v. Federal Savings and Loan Insurance Corp., 589 F.2d 658, 662 (D.C. Cir. 1978).

Until 1991, FDA, by its own regulation, required publication of "interpretive rules and rules of agency practice and procedure." 21 C.F.R. §10.40(d) (1991), repealed May 6, 1991, 56 Fed. Reg. 65 (April 4, 1991).

Neither import alert 66-47 nor the personal import policy is a substantive rule, interpretive rule, or rule of agency practice or procedure that was required to be published. Both were issued to FDA employees as guidance to assist them in the discretionary enforcement of the law. Both the personal import policy andimport alerts are part of the agency's Regulatory Procedures Manual (RPM). The Manual itself provides that statements in the Manual "are not intended to create or confer any rights, privileges, or benefits on or for any private person, but are intended merely for internal guidance." (emphasis added).

A. The FDCA's Provisions for the Regulation and Approval of Drugs

Import alert 66-47 cannot be viewed in isolation from the Congressionally-created system of drug regulation in the United States. To protect the public from drugs that are not safe or effective, Congress enacted a regulatory scheme that requires that any new drug, such as RU486, be approved by FDA before it is distributed or marketed. 21 U.S.C. § 355. To gain such approval, the drug must be the subject of an NDA, which must be reviewed and approved by FDA before it may be introduced into interstate commerce, which includes importation. 21 U.S.C. §§ 355, 331(d). Congress has determined that unapproved drugs shall not be imported into the United States, except pursuant to an IND, even if they have been approved in a foreign country.

To obtain FDA approval of an NDA, the drug sponsor must demonstrate, to FDA's satisfaction, that the drug is both safe and effective for each of it claimed uses. 21 U.S.C. § 355(b). To obtain FDA approval, a sponsor of a new drug must submit: 1) full reports of investigations to establish that the drug is safeand effective; 2) a full list of the drug's components; 3) a full statement of the drug's composition; 4) a full description of the methods, facilities, and controls used for the drug's manufacturing, processing, and packing; 5) samples of the drug and its components; and 6) samples of the proposed labeling for the drug. The drug's sponsor has the burden of proving that the drug is both safe and effective. The bulk of the information submitted to FDA in an NDA usually consists of the reports of clinical (human) and non-clinical (animal) data, describing and analyzing a variety of tests (in vitro, in animals, and in humans), performed by or for the drug's sponsor in an effort to establish the drug's safety and effectiveness.

The clinical data submitted in an NDA is based on testing and research conducted pursuant to an IND. FDA has jurisdiction to assess independently both the validity of the methodology used in such studies and the ultimate questions of safety and effectiveness. Warner-Lambert Co. v. Heckler, 787 F.2d 147, 152-53 (3d Cir. 1986).

B. FDA's Authority Over Drugs Offered For Import and the Personal Import Policy

FDA's authority under 21 U.S.C. § 381(a) to refuse admission of drugs offered for import is extremely broad, reflecting Congress' complete power over imports in general. Sugarman v. Forbragd, 267 F. Supp. 817, 824-25 (N.D. Cal. 1967), aff'd, 405 F.2d 1189 (9th Cir. 1968), cert. denied, 395 U.S. 960 (1969); Board of Trustees of Univ. of Illinois v. United States, 289 U.S. 48, 56-57 (1933); Buttfield v. Stranahan, 192 U.S. 470, 493(1904). There is no unqualified right to import drugs into this country. Sugarman, 267 F. Supp. at 824-25. Indeed, FDA does not need to establish that a drug offered for import actually violates the FDCA in order to refuse admission; any article that "appears" to violate the FDCA may be refused. 21 U.S.C. § 381(a); see Sugarman v. Forbragd, supra; Continental Seafoods v. Schweiker, 674 F.2d 38, 42-43 (D.C. Cir. 1982).

The importation of unapproved new drugs, whether for personal use or otherwise, violates the Act unless the importation is pursuant to an IND. Under certain conditions, however, FDA has, for many years, exercised its discretion to permit the importation of small quantities of unapproved drugs that are not available domestically and are intended for personal use. In 1988, FDA's Office of Regulatory Affairs issued the "Pilot Guidance for Release of Mail Importations" as part of its Regulatory Procedures Manual. Exh. A to Plaintiff's Complaint. The Pilot Guidance provided guidance for allowing the importation of unapproved "articles for treatment of serious and

life-threatening conditions like AIDS and cancer," which are subject to refusal of admission because they are not approved. Id. The Pilot Guidance was issued to help assure uniformity among FDA districts when field personnel use their discretion. Id. at 2.

In December 1989, the agency issued RPM Chapter 9-71, which consolidated the information in the Pilot Guidance and related documents concerning the personal import policy. The personal import policy is by its very terms discretionary. See U.S. Mem.at 9-10. The policy does not provide anyone with a right to import any drug, nor does it require that field personnel use their discretion to examine the background, risk, and purpose of unapproved drugs imported for personal use before making a final decision as to admissibility. See RPM Chap. 9-71-30. The personal import policy provides guidance for use in those instances in which field personnel determine that the exercise of discretion may be appropriate. The policy provides that release of an unapproved drug for personal use may be appropriate if, among other considerations, it is intended for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means, and is not considered to represent an unreasonable risk. Id.

As discussed below, import alert 66-47, which informs FDA personnel that RU486 and other abortifacients are not appropriate for release under this guidance and, therefore, should be initially detained when brought into the country, is simply intended to provide guidance to FDA personnel.

C. Import Alerts and FDA's Import Operations

In general, import alerts are the means the agency uses to identify and disseminate information relevant to imports in order to help ensure a uniform and effective import coverage program. All import alerts are part of the Regulatory Procedures Manual, and are "filed at the end of [] chapter [9-79]." The agency uses import alerts and import bulletins "[t]o identify and disseminate import information (problems, violative trends, etc.) thusproviding a more uniform and effective import coverage program." 9-79-00. Import bulletins are advisory only and provide information, but do "not provide policy or coverage guidance." 9-79-20, 9-79-40. Import alerts "identify problem commodities . . . and provide[] guidance for import coverage," including the identification of products that meet the criteria for automatic detention. 9-79-20. Regulatory Procedures Manual chapter 9-25, issued April 11, 1988, provides guidance regarding automatic detention. It provides:

> Automatic detention is the administrative act of detaining an entry of a specified article without physical examination solely on the basis of information regarding its past violative history and/or other information indicating that the product may be violative. Automatic detention actions are

implemented through the issuance of Import Alerts.

9-25-10. The agency has by regulation stated that if a product appears to be subject to refusal of admission, FDA may detain it and, if the product is detained, FDA will advise the importer of the opportunity to have a hearing. 21 C.F.R. § 1.94. The importer may introduce testimony either orally or in writing. Id. See 21 U.S.C. § 381(a); Sugarman v. Forbragd, 267 F. Supp. at 824. This hearing can take many forms, including telephone conversations and letters. The hearing is the importer's opportunity to present her defense of the importation. RPM Chapter 9-35-40, "Response (Hearing) to Notice of Detention and Hearing." A decision as to the admissibility of detained goods is made only after the importer has an opportunity to present testimony and that testimony is considered. Further, an importermay appeal the decision of the field office to the FDA Commissioner.

D. Import Alert 66-47 Is Not a Rule Requiring Notice and Comment

Consistent with the discussion in the preceding section, import alert 66-47 imposes no new obligations or requirements on either individuals seeking to import RU486 or on FDA personnel, but only informs field personnel that RU486 is an unapproved new drug that can, therefore, be detained and further informs them that it does not meet the criteria of the personal import policy. The FDA need not engage in rule-making procedures to be able to enforce the law in this respect.

Import alert 66-47 does not require field personnel to detain RU486, but instead informs them that statutory authority exists for them to detain shipments or entries identified as RU486 without physically examining them or seeking further information. Even if import alert 66-47 required detention of RU486, refusal of admission is not automatic. If RU486, or any article, is detained -- whether pursuant to an import alert or based on other information -- the importer can request a hearing to challenge the detention, as discussed above. During that proceeding, which can be appealed to the FDA Commissioner, the FDA can reach any decision. That is, the drug can be released based upon the information presented, or a decision may be made to refuse admission. The import alert is not the final agencydecision; the final decision may be that the product should not be refused admission.

Most significantly, the statute, not import alert 66-47, provides the law for the regulation of unapproved drugs. Import alert 66-47 is not "finally determinative" of whether a particular importation of RU486 violates the Act. See Pacific Gas & Electric v. FPC, 506 F.2d 33, 38 (D.C. Cir. 1974). The ultimate decision on the admissibility of RU486 would not be based upon the import alert, it would be based upon the statute. That is, FDA would examine whether RU486 appears to be

unapproved or otherwise in violation of the Act, not whether RU486 was subject to an import alert. Import alerts are themselves not binding on the agency or the public, and FDA cannot rely on an import alert, by itself, in a final decision excluding a drug. In other words, they are not the law.

Thus, as guidance advising FDA personnel and the public of the manner in which the agency intends preliminarily to exercise its discretion, import alerts are exempt from the notice-and-comment rulemaking procedures of the APA. Many courts have recognized that guidance documents similar to the import alert are not subject to notice and comment. In Brock v. Cathedral Bluffs Shale Oil Co., 796 F.2d 533 (D.C. Cir. 1986), the courtheld that "Enforcement Policy and Guidelines for Independent Contractors," which were used a "guidance in making individual enforcement decisions," were not required to be published. Id. at 535-38. In American Mining Congress v. Marshall, 671 F.2d 1251 (10th Cir. 1982), the court held that a "strategy" outlining how the Secretary planned to enforce a standard was not required to be published. Id. at 1262-63. The Fifth Circuit, in Southeastern Minerals, Inc. v. Harris, 622 F.2d 758 (5th Cir. 1980), recognized that FDA Compliance Policy Guides (CPGs) do not require rulemaking procedures. Id. at 766. See also Cowdin v. Young, 681 F. Supp. 366, 370 (W.D. La. 1987) (CPGs are not binding legal requirements); see also Panhandle Producers v. EPA, 847 F.2d 1168, 1174-75 (5th Cir. 1988) (Economic Regulatory Administration guidelines relating to approval of natural gas imports were statements of policy, not binding rule; rulemaking not required); Mercury Motor Express, Inc. v. United States, 648 F.2d 315, 319 (5th Cir. 1981) (ICC order announcing new criteria for approving for-hire operating authority applications was policy statement).

Plaintiff relies heavily on Bellarno International Ltd. v. FDA, 678 F. Supp. 410 (E.D.N.Y. 1988). This reliance is misplaced. As an initial matter, Bellarno's conclusion that an import alert required publication is simply incorrect, for the reasons stated above -- an import alert is simply a preliminary step in the administrative process, and not a binding legal decision. Even if this were not the case, however, the facts inBellarno are distinguishable from the facts in this case in a critical respect. Most significantly, the import alert in Bellarno contained a requirement that went beyond satisfaction of the statutory standard applicable to all drugs imported into the United States. The import alert there also required proof of five additional elements. The Bellarno court found that the agency had created a new obligation (i.e., acquiring and maintaining a paper chain of custody) with which importers had to comply to satisfy the statutory requirements. 678 F. Supp. at 414 & n.4. In the instant case, no such obligation has been created: enforcement of the statutory requirement to have an approved NDA or IND to import a drug product does not impose any

new standards or requirements on RU486. It is undeniable that, under the plain meaning of the statute, importation of RU486 is illegal absent an IND. Neither the personal use policy nor the import alert change that fact; hence, the import alert does not create any "rights and obligations" beyond the statute. The RU486 import alert only provides guidance regarding initial steps in the enforcement of the statute with respect to RU486. Therefore, the specific facts in Bellarno prevent any useful comparison between the two cases.

Import alert 66-47 does not fit into any of the categories of rules requiring publication. A recent case from in this Circuit shows that the import alert is not a substantive rule. In New York City Employees' Retirement System v. SEC, 45 F.3d 7 (2d Cir. 1995), the court followed a test (laid out originally bythe D.C. Circuit) to determine whether a rule has "legal effect" and is therefore "legislative." Id. at 13. If any of these four criteria are met, it is an indication that the rule is legislative:

> (1) in the absence of the rule, no legislative basis would exist for an enforcement action; (2) the agency has published the rule in the Code of Federal Regulations; (3) the agency explicitly invoked its general legislative authority to pass the rule; (4) the rule effectively amends a prior legislative rule.

Id. at 13. See American Mining Congress v. Mine Safety & Health Admin., 995 F.2d 1106, 1112 (D.C. Cir. 1993).

Under this test, the import alert is clearly not a legislative rule: In its absence, there would be an adequate legislative basis to exclude unapproved drugs from import (the Food, Drug, and Cosmetic Act); it was not published in the CFR; the FDA did not invoke its legislative authority; and the rule did not amend a prior legislative rule.

Nor is import alert 66-47 an interpretative rule; it does not explain or define any provision of the Act. See New York City Employees' Retirement System v. SEC, 45 F.3d at 12 (interpretive rules "'clarify an existing statute orregulation.'" (quoting White v. Shalala, 7 F.3d 296, 303 (2d Cir. 1993)). Nor does it outline a rule of agency practice or procedure; it is simply guidance for the exercise of discretion.

For these reasons, no law required that the import alert for RU486 be published for notice and comment, and plaintiff's arguments to the contrary must be rejected.

III. THE IMPORT ALERT IS CONSISTENT WITH THE FDCA AND IS REASONABLE.

Even if the Court were to determine that jurisdiction existed for it to examine the merits of import alert 66-47, it is reasonable and must be upheld.

In reviewing this action, the Court must first determine

whether Congress has spoken directly to the question at issue. Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842 (1984). If the intent of Congress is clear, "that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent ofCongress." Id. at 842-43 (footnote omitted). Significantly, this case involves an issue on which Congress has spoken directly and without ambiguity. Congress has made it illegal to import unapproved new drugs into this country except under an IND, and the RU486 import alert is based on this fact. For this reason, the RU486 import alert must be upheld and no further inquiry into this matter is necessary or required. This agency action is consistent with the statute and, as noted in the defendants' motion to dismiss, committed to the discretion of the agency.

If, however, this Court were to examine the matter further, the RU486 import alert is reasonable and not arbitrary or capricious. Under the "arbitrary and capricious" standard, judicial review of agency action is narrowly circumscribed:

> [T]he Court must consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment. ... Although this inquiry into the facts is to be searching and careful, the ultimate standard of review is a narrow one. The Court is not empowered to substitute its judgment for that of the agency.

Citizens to Preserve Overton Park v. Volpe, 401 U.S. 402, 416 (1971) (citations omitted). See also Bowman Transportation Co. v. Arkansas-Best Freight System, Inc., 419 U.S. 281, 285-86 (1974).

Great deference is given to the agency. Chevron U.S.A., 467 U.S. at 844. Further, if the agency's choice "represents a reasonable accommodation of conflicting policies," it is not to be disturbed unless "it appears from the statute or its legislative history that the accommodation is not one thatCongress would have sanctioned." Id. at 845 (emphasis added). See also Udall v. Tallman, 380 U.S. 1, 16-17 (1965); Bowles v. Seminole Rock & Sand Co., 325 U.S. 410, 413-14 (1945).

This is less than a substantial evidence test, or even a preponderance of the evidence test. See, e.g., Ethyl Corp. v. EPA, 541 F.2d 1, 37-38 (D.C. Cir.), cert. denied, 426 U.S. 941 (1976); Action For Children's Television v. FCC, 564 F.2d 458, 478 (D.C. Cir. 1977); Henley v. FDA, 873 F. Supp. 776, 782 (E.D.N.Y. 1995). The FDA's decisions must be presumed to be valid. It is plaintiff's burden to demonstrate that there is no rational basis for the decisions. Even if this Court were to determine that there were other actions that the FDA could have

taken that would have been, in the Court's view, preferable, the Court may not substitute its judgment for that of the FDA nor interject itself into the area of discretion reserved for the agency. Chevron U.S.A., 467 U.S. at 843 n.11. See also Mourning v. Family Publications Service, Inc., 411 U.S. 356, 371-72 (1973); New York Dep't of Social Services v. Shalala, 21 F.3d 485, 492 (2d Cir. 1994). "As this standard indicates, the scope of our review is relatively narrow. There will be occasions when 'we must affirm decisions with which we disagree' as long as they are rational and reflect a full consideration of relevant factors." National Industrial Sand Ass'n v. Marshall, 601 F.2d 689, 699 (3d Cir. 1979) (footnote omitted). Deference is especially important here: "[T]he Court is mindful that when it reviews agency action that is based upon scientific inquiry andtechnical expertise, a high degree of deference is appropriate." Henley v. FDA, 873 F. Supp. at 782.

Under this narrow and deferential scope of review, plaintiff's challenge must be rejected. The RU486 import alert is reasonable, fully consistent with the FDCA, and not arbitrary or capricious.

A. The Issuance of Import Alert 66-47 was Reasonable and Consistent with the FDCA

FDA's Director of Field Investigations issued an "Import Bulletin" for RU486 on September 26, 1988. Exh. C to Plaintiff's Complaint. This Bulletin informed FDA field personnel that because RU486 was not consistent with the criteria of the "Pilot Guidance for Release of Mail Importations," which was issued on July 20, 1988, it should not be allowed admission into the United States pursuant to that Pilot Guidance. Id. As discussed in section II, FDA's Office of Regulatory Affairs had issued that Pilot Guidance on a trial basis to provide guidance for allowing the importation of unapproved "articles for treatment of serious and life-threatening conditions like AIDS and cancer." Exh. A toPlaintiff's Complaint. The Pilot Guidance noted that individuals had been purchasing unapproved products from foreign sources for these life-threatening conditions, and that such products are subject to refusal of admission because they are not approved. Id. The Pilot Guidance was, by its very terms, discretionary. Id. at 2. The original purpose of this guidance was to allow treatment for diseases that would lead to severe debilitation or death if untreated and for which adequate treatment was not currently available. The personal use of RU486 as an abortifacient does not fall within this purpose.

The agency replaced this import bulletin with an import alert on June 6, 1989. Exh. D to Plaintiff's Complaint. The import alert reiterated that importation of abortifacients such as RU486 was inappropriate under the Pilot Guidance. Id. at 2. It also stated that "[t]he intended use of such drugs could pose a risk to the safety of the user." Id.

The import alert was prompted by publicity concerning the

use of RU486 as an abortifacient that led FDA to believe that the drug might be imported for commercial purposes or for unsupervised or clandestine use. See Letter from James Benson to Ron Wyden, Exh. E to Plaintiff's Complaint ("Exh. E") at 2; RU486: The Import Ban and Its Effect on Medical Research: Hearing Before the House Subcommittee on Regulation, Business Opportunities, and Energy of the Committee on Small Business, 101st Cong., 2d Sess. 36, 41, 175-78 (1990) (hereinafter "RU486 Hearings") (partially reprinted at Exh. H to Plaintiff'sComplaint. This reasoning was based on inquiries from the public and FDA field offices about this drug, the history of misuse of abortifacients, and uncertainty about whether supervision by physicians would occur. See Exh. E at 2; RU486 Hearings at 42-43; 175-78. See also Letter from Frank Young to Robert Dornan, Exh. G to Plaintiff's Complaint ("Exh. G").

The agency revised the import alert on April 17, 1990, to encompass the known chemical names for RU486, and to refer to RPM Chapter 9-71, issued December 11, 1989, which consolidated the information in the Pilot Guidance and related documents concerning the personal import policy. The revised Import Alert repeated the statements in the original import alert concerning the inappropriateness of releasing abortifacients under the personal importation policy.

The primary rationale for the Import Alert was that RU486, as well as other abortifacients, pose an unacceptable safety risk because, by their very nature, the drug would likely be used without supervision, and such unsupervised use could be hazardous to health. See Exh. E; RU486 Hearings at 175-78. Additionally, RU486 is generally used in conjunction with another drug, a prostaglandin, which is also not approved for this use in the United States. See Exh. E; RU486 Hearings at 175-78.

Use of RU486 as an abortifacient can result in "uterine bleeding, severe nausea, vomiting, and weakness, which might require prompt medical intervention." See Exh. G; Patient Informed Request, Exhibit B-3 to plaintiffs' motion for preliminary relief. In France, where the distribution and use of RU486 is highly regulated, RU486 is used in accordance with a strict regime under close medical supervision. In this medically-supervised environment, use of RU486 is frequently accompanied by a variety of side effects. These side effects, which occur primarily after administration of the prostaglandin, include cramps and abdominal pain similar to those associated with a very heavy period, nausea, vomiting, and/or diarrhea that sometimes require medical attention, and uterine bleeding that can last as long as three weeks. Attachment A hereto at 3 and clinical information attached thereto at 2. One of plaintiff's exhibits states that about one percent of women in a French report required treatment to control bleeding. Exhibit B-4 to plaintiffs' motion for preliminary relief, at 275. This source

also noted three cases of major cardiovascular complications, and that postabortion bleeding is more prolonged after medical abortion than surgical abortion. Id. at 275-76. See also Exh. B-5 at 48 (4 to 5 percent of women had heavy bleeding). When used in accordance with a strict regime, RU486 has a failure rate of about 4 in 100 (ongoing pregnancy in 1 of 100 attempts, incomplete terminations in 3 of 100 attempts). In such instances, a vacuum aspiration or curettage is necessary toterminate the pregnancy. Attachment A hereto at 3 and clinical information attached thereto at 3; see also Patient Informed Request, Exhibit B-3 to Plaintiffs' motion for preliminary relief.

Further, serious cardiovascular complications have occurred in women, including one fatality, when RU486 is used with certain prostaglandins that are no longer used in controlled settings, Attachment A hereto at clinical information attached thereto at 2, but might be used inadvertently in a less well-supervised environment.

These potential complications can be monitored and treated in a controlled clinical trial, but not in the context of personal use. In issuing the import alert, the agency was concerned not only with the risks of RU486, but also with the fact that RU486 does not meet the criteria of the personal import policy. The relevant portion of the personal import policy contains two parts which describe the situations in which it may be appropriate for field personnel to consider releasing an unapproved drug for personal use. RPM Ch. 9-71-30(C).

The first part of the policy applies to unapproved drugs that are not intended for the treatment of a serious condition and are not known to represent a significant health risk. See RPM 9-71-30(C). This provision is intended for such drugs as cold medications that a person might buy abroad to treat a minor illness while traveling and bring back into the United States. Exh. H to Plaintiff's Complaint at 36. RU486 does not qualifyunder this provision because it is used for a serious condition and because its use, as discussed above, represents a significant health risk.

The second part of the policy applies to unapproved drugs that are, among other considerations, intended for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means, and are "considered not to represent an unreasonable risk." RPM Ch. 9-71-30(C). RU486 does not fall within this provision because it is proposed for use in treating a condition for which an alternative treatment does exist and because it poses a safety risk. Id.; RU486 Hearings at 36. Other means of abortion are available in the United States, and RU486 is not necessary to make abortion available. See RU486 Hearings at 36. Moreover,RU486 is available in controlled clinical trials at the present time.

B. The Relief Plaintiff Seeks Is Inconsistent With the FDCA and Long-Standing Principles of Deference to FDA's Expertise

Evidently acknowledging that inadequately supervised use of RU486 as an abortifacient poses serious risks to health, plaintiff requests that this Court require the agency to permit the importation of RU486 for personal use as an abortifacient under medical supervision. It is not clear whether plaintiff is asking the Court to reject the agency's conclusion that personal importation is inappropriate even if an individual identifies a physician responsible for her treatment, or whether plaintiff is proposing that FDA become actively involved in controlling how RU486 is used and administered for personal use as an abortifacient.

The former scenario is inconsistent with long-standing principles of deference to FDA's expertise and judgment in matters involving the public health and safety. The latter would require FDA to create and administer a system of medicalcontrols for the use and administration of an unapproved new drug independent of its statutorily mandated system for regulating the investigational use of unapproved new drugs. 21 U.S.C. § 355(i); 21 C.F.R. Part 312. Although, by statute and regulation, FDA can regulate the conditions for use for investigational drugs covered by an IND, no controls exist to minimize the risks associated with the use of unapproved drugs imported by individuals for personal use. In order to minimize the risks associated with the use of RU486 as an abortifacient, a physician must know many things about the use and effects of RU486 and prostaglandins. As a result, to release RU486 for personal use as an abortifacient under medical supervision in a manner consistent with FDA's concerns would require significantly more than a physician's name and address. Active supervision by FDA in the personal use of an unapproved drug would require FDA to devote significant resources to such supervision rather than to the process by which the agency evaluates and approves drugs.

As discussed in Section II, the FDCA's drug approval scheme is the mechanism by which new drugs can be approved and legally marketed and distributed. Plaintiff is using this litigation in an attempt to circumvent the Congressionally established procedure for drug approvals, and to have this Court examine the safety and effectiveness of RU486. In so doing, plaintiff blatantly ignores the fact that only the FDA has the authority to determine whether a drug is safe and effective. Premo Pharmaceutical Laboratories, Inc. v. United States, 629 F.2d 795, 803-04 (2d Cir. 1980). Thus, despite plaintiff's numerous assertions that RU486 is "safe" and "effective" for use as an abortifacient, this court lacks authority to make such a finding. For all of these reasons, even if reviewable, import alert 66-47 is reasonable and must be upheld.

IV. THE IMPORT ALERT IS CONSTITUTIONAL

BECAUSE IT HAS NEITHER THE PURPOSE NOR THE EFFECT OF BEING AN UNDUE BURDEN ON PLAINTIFF'S ABILITY TO CHOOSE TO TERMINATE A PREGNANCY

The plaintiff's claim that an import alert on RU486 violates her constitutional right to privacy lacks merit. The Constitution does not preclude the government from regulating medical care, including abortion. Further, the Supreme Court has repeatedly held that the government has a legitimate interest in protecting the health of women seeking abortions.

The ability to choose abortion before viability of the fetus is a constitutional right. See Planned Parenthood of Southeastern Pennsylvania v. Casey, 112 S.Ct. 2791 (1992); Webster v. Reproductive Health Services, 492 U.S. 490 (1989); Thornburgh v. American College of Obstetricians and Gynecologists, 476 U.S. 747 (1986); Akron v. Akron Center For Reproductive Health, Inc., 462 U.S. 416 (1983); Roe v. Wade, 410 U.S. 113 (1973). In Casey, the Supreme Court reaffirmed "Roe's essential holding" that the Due Process Clause of the Fourteenth Amendment protects a substantive liberty interest that encompasses a right to choose to terminate a pregnancy. Casey, 112 S.Ct. at 2803-05. Casey further reaffirmed the principle that the government may regulate abortion in certain circumstances.

The issue is whether import alert 66-47 imposes an undue burden on a woman's ability to choose to terminate her pregnancy. An undue burden is a governmental action "that has the purpose or effect of placing a substantial obstacle in the path of a woman seeking an abortion of a nonviable fetus." Id. at 2821 (emphasis added). As explained below, the import alert has no such purpose or effect and, therefore, passes constitutional scrutiny.

A. The Import Alert Is Reasonably Related to the Preservation and Protection of Health

In Casey, the Supreme Court distinguished between those government actions that have legitimate purposes and those that substantially restrict a woman's right to choose to terminate her pregnancy with the sole purpose of impeding abortion. The Court reiterated that the government has a legitimate interest in protecting the health of a woman seeking an abortion. 112 S.Ct. at 2804; see Roe v. Wade, 410 U.S. at 150 (government "has a legitimate interest in seeing to it that abortion . . . is performed under circumstances that insure maximum safety"). The import alert serves legitimate and important purposes "reasonably directed to the preservation and protection of maternal health." Planned Parenthood of Central Missouri v. Danforth, 428 U.S. 52, 80 (1976), citing Roe v. Wade, 410 U.S. at 163.

Unapproved drugs violate the FDCA. Drugs that appear to be unapproved may be refused entry pursuant to 21 U.S.C. § 381(a).

Products known to be unapproved new drugs may, therefore, be the subject of an import alert. The issuance of import alerts is a routine FDA action. The fact that FDA has issued over forty import alerts based on the absence of an approved NDA shows that FDA did not subject RU486 to any special treatment or standards. Import alerts serve a compelling government interest that is entirely unrelated to abortion: they provide field personnel with information concerning illegal products so that the public will not be exposed to them. The import alert in question here does not interfere with the right to choose abortion. Its principal purpose is to prevent unapproved drugs such as RU486 from being used in uncontrolled and potentially hazardous circumstances.

The import alert exists because the safety and effectiveness of RU486 has not been demonstrated to the FDA, and FDA is concerned about the potential for harm associated with the inadequately controlled or unsupervised use of RU486 as an abortifacient. Existing information about RU486 indicates that use of RU486 as an abortifacient must follow a precise regimen, and frequently results in a number of side effects, including cramps, abdominal pain, nausea, vomiting, and uterine bleeding that can last as long as three weeks. In some cases, the bleeding is severe enough to require a blood transfusion. For all of these reasons, the import alert is reasonably related to the preservation and protection of health.

By contrast, the prohibition on saline amniocentesis that the Supreme Court invalidated in Danforth did not have legitimate public health purposes, but instead had as its motive the restriction of abortion. Danforth, 428 U.S. at 79. At the time, saline amniocentesis was the method of abortion "most commonly used nationally by physicians after the first trimester." Id. at 78. The Court found the remaining abortion methods available to women in Missouri, such as hysterotomy and hysterectomy, were actually more dangerous to health than the method prohibited on safety grounds, and further found that the prohibition had the effect of inhibiting the vast majority of abortions after the first twelve weeks. Id. at 76-79.

However, RU486 is not a method of abortion commonly used in the United States, although it is being used in limited number of well-controlled clinical studies within United States. Further, although the plaintiff asserts "the proven safety of RU486 as an abortifacient," Pl. Mem. at 16, this assertion is conclusory. As discussed above, it cannot be said that RU486 is safe and effective, let alone safer or more effective than surgical abortions.

Unlike the governmental action at issue in Danforth, the import alert does not have the purpose or the effect of substantially interfering with the right to abortion. Commonly used methods of abortion remain available. An import alert onRU486 is entirely different from the ban on saline amniocentesis in Danforth, and upholding this alert would not

allow the government to "ban commonly used methods of early surgical abortion." Pl. Mem. at 15. Despite the plaintiff's assertions to the contrary, the import alert was instituted to prevent RU486, an unapproved drug, from being used in uncontrolled and potentially hazardous circumstances.

B. The Import Alert On RU486 Does Not Impose An Undue Burden On A Woman's Right To Choose Abortion

The Supreme Court has recognized that many health regulations "might have the incidental effect of increasing the cost or decreasing the availability" of abortions. Casey, 112 S.Ct. at 2819. However, a governmental action that "serves a valid purpose" will not be invalidated simply because it has "the incidental effect of making it more difficult or more expensive to procure an abortion." Id. Consequently, "[r]egulations designed to foster the health of a woman seeking an abortion are valid if they do not constitute an undue burden." Id. at 2820-21. The import alert creates no burden at all; it prohibits no one from having an abortion, and is designed to foster women's health.

The plaintiff argues that it is insufficient that traditionally accepted methods of abortion remain available, and that any ban on any method of abortion is unconstitutional. Pl. Mem. at 13, 15. The plaintiff further contends that the import alert constitutes a substantial obstacle to a woman seeking an abortion because it curtails a woman's right to determine thecourse of her own medical treatment in that it prevents women from employing a non-surgical method of abortion. Pl. Mem. at 14.

Under plaintiff's theory, the government could not prohibit any unsafe abortion techniques, and the FDA would be powerless to prevent untested and potentially dangerous or ineffective drugs and medical devices from being sold and used simply because they relate to abortion. Plaintiff's position is not the law.

Although an individual's decision whether or not to have medical treatment is generally a protected right, her ability to select a particular type of treatment, especially when it involves the use of a particular medication, is within the area of governmental interest in protecting the public health. Rutherford v. United States, 616 F.2d 455, 457 (10th Cir. 1980). An individual does not have a constitutional right to obtain a particular type of treatment or to obtain treatment from a particular provider if the government has reasonably prohibited that type of treatment or provider. Mitchell v. Clayton, 995 F.2d 772, 775 (7th Cir. 1993). That the governmental action at issue affects a woman's decision to choose abortion does not alter this principle. See Connecticut v. Menillo, 423 U.S. 9, 11 (1975) (no constitutional right to an abortion by a non-physician); Roe v. Wade, 410 U.S. at 150, 165 (same); see also Casey, 112 S.Ct. at 2819-20 (a woman does not have an absolute right to an abortion).

The import alert does not create a prohibition on RU486. Rather, the FDCA makes it illegal to import unapproved new drugs such as RU486 into this country, and the import alert simply recognizes this fact. Courts have consistently held that the new drug approval system established by Congress and enforced by FDA is constitutional, and that an individual does not have a right to obtain an unapproved drug. Rutherford, 616 F.2d at 457; Carnohan v. United States, 616 F.2d 1120, 1122 (9th Cir. 1980); Duncan v. United States, 590 F. Supp. 39, 42-44 (W.D. Okla. 1984); Kulsar v. Ambach, 598 F. Supp 1124, 1126 (W.D.N.Y. 1984); United States v. Vital Health Products, Ltd., 786 F. Supp. 761, 777-78 (E.D. Wis. 1992), aff'd sub nom. United States v. LeBeau, 985 F.2d 563 (7th Cir. 1993). The reasonableness of the statutory and regulatory scheme is bolstered by the fact that the investigational new drug provisions permit access to unapproved drugs, such as RU486, in controlled clinical settings.

Constitutional protection for RU486 would inevitably mean constitutional protection for other unproven, potentially dangerous methods of abortion. The potential for harm to health is great, and the government's interest in preventing this outcome and preserving the public protection now afforded by the FDCA, is significant. The import alert, which permits women to use other abortion methods, does not unduly burden a woman's right to choose abortion and is, therefore, constitutional.

CONCLUSION

For the foregoing reasons, plaintiff's complaint should be dismissed, or judgment should be granted in favor of the defendants.

Respectfully submitted,

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Date: June 30, 1995

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK: IAS PART 53

DANCO LABORATORIES,

Plaintiff,

Index No. 602406/97

-against-

CHEMICAL WORKS OF GEDEON RICHTER, LIMITED,

Defendant.

Charles Edward Ramos, J.S.C.:

This is an action for breach of contract, fraud, negligent misrepresentation and prima facie tort by plaintiff Danco Laboratories ("Danco") against defendant Chemical Works of Gedeon Richter Limited ("Gedeon") in connection with a contract to manufacture mifepristone, also known as RU-486, a drug which is used to induce nonsurgical abortions. In a decision dated May 28, 1998, this court denied a motion by The Washington Post Company ("Post") to intervene in this action. The court also declined to vacate its order dated July 30, 1997, which sealed the record in this case. In a decision dated December 8, 1998, the Appellate Division, First Department, modified the May 28th order to the extent of granting the motion to intervene to the extent of "remanding this matter to the trial court for an expedited de novo determination, upon written submissions, and the issuance of a written decision which shall detail the grounds underlying any finding of 'good cause' in accordance with the provisions of Rule 216.1 (22 NYCRR 216.1)."