ORIGINAL

ORIG AMENDMENT

The Danco Group

July 14, 1999

Reviewed. See Chem. Rev. #3.

/S/ 2/19/00

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 15 1999
HFD-580

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 029 - Responses to FDA Approvable Letter of September 18, 1996

Dear

This Amendment 029 provides responses to ten (10) of the nineteen (19) points raised by the FDA in their Approvable Letter dated September 18, 1996. Subsequent filings will respond to the remaining nine (9) points.

For ease of review, this Amendment separately refers to each one of the nineteen (19) points raised and either provides the response, provides a reference to a previous response or indicates that the response will be provided. Responses still to be provided relate to "Drug Product" (4), "Drug Substance" (1), "Safety" (1), "Phase IV Commitments" (1), "Distribution" (1) and "Promotion" (1) and are planned for submission in the near future.

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

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

Sincerely,

President and
Chief Executive Officer

This document constitutes trade secret and confidential commercial information exe 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

/dns
Enclosure

CC: [redacted]

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

[redacted]

[redacted] – FDA

NDA 20-687: Mifepristone Tablets, 200 mg
The Population Council

Robbins, Ph.D., Ann (September 18, 1996)

Point #12

COMMENT: "Drug Substance:

2. We recommend that an assay method for be developed and submitted along with appropriate proposed limits."

RESPONSE: A chromatographic method has been developed for the assay of by Shanghai HuaLian Pharmaceutical Company, Limited, which is our current source of substance.

This method is currently being validated.

For your reference, we are herewith providing the details of the chromatographic method and attaching an exhibit chromatogram for a recent lot of

Details of Chromatographic Method:

Column:
Mobil Pha
Detector:
Flow Rate

Sample Solution:

Injection Volume:

Analytical Time:

August, 1999

ORIGINAL

The Danco Group

ORIG AMENDMENT

June 30, 1999

Reviewed - See Chem. Rev. #3
/S/
2/19/00

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 028 - Chemical, Manufacturing, and Controls (CMC) Section I for Drug Substance: **Supplement**

Dear ———

In connection with our submission of June 3, 1999, we are herewith enclosing, in duplicate, a supplement to the CMC Section submitted as Amendment 025.

This amendment 028 includes the following:

- Annex 1: Mifepristone ———
- Annex 2: ———

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

Thank you for your attention.

/S/

President and
Chief Executive Officer

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☒ N.A.I. ☐ MEMO
DATE 2/19/00
CSO INITIALS /S/

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

/dns
Enclosure

CC:

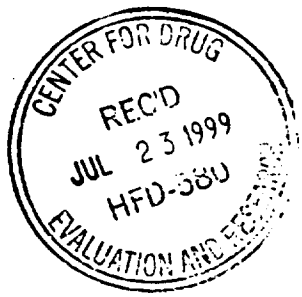
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

[redacted] FDA

ORIG AMENDMENT

The Danco Group

July 22, 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, MD 20857

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 030 - Additional Responses to "FDA Approvable Letter of September 18, 1996"

Dear

In our previous Amendment 029 we responded to ten (10) of the nineteen (19) points raised by the FDA in the Approvable Letter dated September 18, 1996. All nineteen (19) points were identified and numbered in that submission.

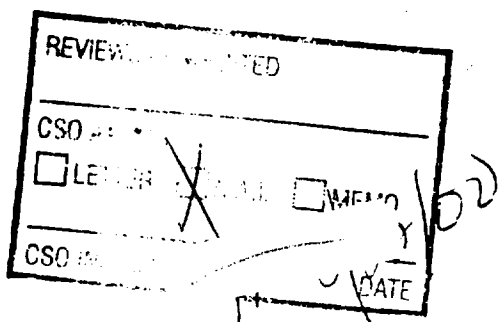
This Amendment 030 provides responses to the four (4) points relating to "Drug Product"; numbers 5, 6, 15 and 18 (as numbered in our Amendment 029). In addition, we have added to the prior response on one (1) "Drug Substance" point, number 2. This brings our responses to date to fourteen (14) of the total of nineteen (19) points raised in the Letter.

The five (5) responses still to be provided relate to "Drug Substance" (1), "Safety" (1), "Phase IV Commitments" (1), "Distribution" (1) and "Promotion" (1).

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

Sincerely

President and
Chief Executive Officer



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

/dns
Enclosure

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 22, 1999
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):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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)

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

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Second Response to FDA Approvable Letter of Sept. 18, 1996.

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmidt for	Sandra P. Arnold, Vice President	July 22, 1999

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)

MIF 007249

ORIGINAL

ORIG AMENDME

The Danco Group

July 14, 1999

Reviewed. See Chem. Rev. #3.

2/19/00

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 029 - Responses to FDA Approvable Letter of September 18, 1996

Dear

This Amendment 029 provides responses to ten (10) of the nineteen (19) points raised by the FDA in their Approvable Letter dated September 18, 1996. Subsequent filings will respond to the remaining nine (9) points.

For ease of review, this Amendment separately refers to each one of the nineteen (19) points raised and either provides the response, provides a reference to a previous response or indicates that the response will be provided. Responses still to be provided relate to "Drug Product" (4), "Drug Substance" (1), "Safety" (1), "Phase IV Commitments" (1), "Distribution" (1) and "Promotion" (1) and are planned for submission in the near future.

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

Sincerely,

BC

President and
Chief Executive Officer

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

This document constitutes trade secret and confidential commercial information e ...m public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any ... 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

/dns
Enclosure

CC:

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	July 14, 1999
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):*

1230 York Avenue
New York, NY 10021

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
x	19. OTHER (Specify) Initial Response to FDA Approvable Letter of Sept. 18, 1996

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmidt for	Sandra P. Arnold, Vice President	07/14/99

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

ORIGINAL

The Danco Group

ORIG AMENDMENT

June 30, 1999

Reviewed - See Chem. Rev. #3

2/19/00

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 028 - Chemical, Manufacturing, and Controls (CMC) Section I for Drug Substance: **Supplement**

Dear [redacted]

In connection with our submission of June 3, 1999, we are herewith enclosing, in duplicate, a supplement to the CMC Section submitted as Amendment 025.

This amendment 028 includes the following:

- Annex 1: [redacted]
- Annex 2: [redacted]

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

Thank you for your attention.

Sincerely,

[redacted]

President and
Chief Executive Officer

REVIEWS COMPLETED
CDC ACTION
☐ LETTER ☒ E-MAIL ☐ MEMO
CDC INITIALS
DATE 2/20/00

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	June 30, 1999
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):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

CODE NAME *(If any)*

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

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

APPLICATION INFORMATION

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

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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)

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

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmidt for	Sandra P. Arnold, Vice President	06/30/99

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

Please **DO NOT RETURN** this form to this address.

FORM FDA 356h (7/97)

MIF 007257

ORIGINAL

The Danco Group

ORIG AMENDMENT

June 15, 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, MD 20857

Reviewed See Chem. Rev. #3

2/19/00

Re: NDA 20-687, Mifepristone 200mg Oral Tablets
- Amendment 026 - Proposed Drug Product Manufacturing Procedure

Dear

During a telephone discussion on Friday, June 11 with requested Danco to provide the FDA with the manufacturing process that Danco will follow to produce the demonstration and validation batches of Drug Product. We are enclosing this documentation as Amendment 026.

This process is identical to the original Roussel process but, based on our experience during the upcoming production of the demonstration and validation batches, may need minor adjustments which will be reflected in Danco's subsequent Drug Product CMC submission.

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

Sincerely,

/S/

President and
Chief Executive Officer

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, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

/cns
Enclosure

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	June 15,1999
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):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

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

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

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

APPLICATION INFORMATION

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

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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

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 007260

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

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmitz for	Sandra P. Arnold, Vice President	06/15/99

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

Please DO NOT **RETURN** this form to this address.

FORM FDA 356h (7/97)

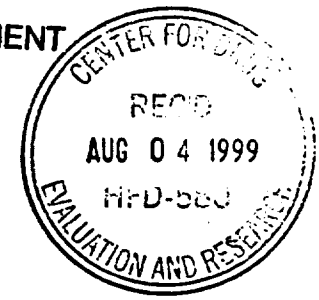
MIF 007261

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

August 3, 1999

ORIG AMENDMENT



mailed 8/5/99 151

VIA FEDERAL EXPRESS

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 200 mg Oral Tablets
Amendment 031 - Additional Response to "FDA Approvable Letter of September 18, 1996"
- Safety Update Report #2

Dear [redacted]

Reference is made to Amendment 030 dated July 22, 1999 which lists the remaining five (5) points to be answered for the Approvable Letter of September 18, 1996. This submission is in response to the point on **Safety Information** noted in Amendment 030 as being outstanding.

This second NDA Safety Update Report includes accumulated information relative to the safety of mifepristone which has been obtained by the Population Council since May 15, 1996, the cut-off date for the first Safety Update Report submitted on June 20, 1996. The cut-off date for this second report is June 30, 1999. The submission consists of an archival copy and a duplicate clinical review copy.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the French manufacturers, Roussel Uclaf and Exelgyn Laboratories. Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and international product labeling, and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by Exelgyn and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

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

The Population Council maintains [redacted] mifepristone and this Safety Update Report #2 includes information that has been previously provided in the IND. We ask that the IND be incorporated by reference in this NDA.

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

Very truly yours,

Sandra Arnold

cc:

SPA: lm

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Population Council	August 3, 1999
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):* 1230 York Avenue New York, NY 10021	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

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

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

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (Chemical Abstracts) - (11β,17β)-11-[(4-Dimethylaminophenyl)-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

CODE NAME *(If any)*

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

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

APPLICATION INFORMATION

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

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, 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 ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

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

NUMBER OF VOLUMES SUBMITTED 5 (in duplicate) THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA Approvable Letter of Sept. 18, 1996,

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Frederick H. Schmitt for	Sandra P. Arnold, Vice President	08/03/99

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

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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

Please **DO NOT RETURN** this form to this address.

Table of Contents

Safety Update Report #2
NDA 20-687

Table of Contents (Cont.)

Safety Update Report #2
NDA 20-687

Table of Contents (Cont.)

Safety Update Report #2
NDA 20-687

INTRODUCTION

This second NDA Safety Update Report includes accumulated information relative to the safety and efficacy of mifepristone which has been obtained by the Population Council since May 15, 1996, the cut-off date for the first safety update report submitted on June 20, 1996. The cut-off date for this second report is June 30, 1999.

Information in the report includes that obtained from recently completed and ongoing clinical trials with the product sponsored by the Population Council and by the French manufacturers, Roussel Uclaf and Exelgyn Laboratories. Additionally, the report contains Periodic Safety Update Reports prepared by the French manufacturers to summarize the worldwide safety experience with the product, updated information on international regulatory approvals and international product labeling, and new information obtained from the literature. The report also contains a Clinical Expert Report on mifepristone which was prepared by Exelgyn and which summarizes the accumulated clinical documentation on the efficacy and safety of the product.

*** ***

General principles observed in the assembly of this submission are as follows:

Volumes are bound, titled and numbered in accordance with FDA recommendations. Within each volume, pages are numbered consecutively with Page 1 as the first page of the informational content of each volume. Page numbers are located in the lower right corner of each page.

To facilitate location of information within the submission, a copy of the Table of Contents for the complete submission is included in Volume One and also included at the beginning of each volume in the submission. Within the submission, the informational contents are segmented using tabbed inserts to identify major subdivisions. Within these subdivisions, significant segments of information are further indicated by colored dividers to create the following organizational hierarchy.

Volume
Tabbed Insert
Blue 60# Page Insert
Yellow 20# Page Insert

NEW NONCLINICAL PHARMACOLOGY/TOXICOLOGY INFORMATION

The Population Council has sponsored no nonclinical pharmacology/toxicology studies with mifepristone and has received no new reports of completed studies since submission of NDA Safety Update #1.

NEW CLINICAL INFORMATION

Table of New Investigations

A updated listing of known recently completed or ongoing clinical trials is presented in **Table 1**. The table is revised from that presented in NDA Safety Update #1 to indicate that the final reports for Studies PC 166A and B, conducted in this country under the sponsorship of the Population Council, are complete and were submitted to the FDA on June 3, 1999 (NDA 20-687/Amendment 024). Additionally, the table now includes three studies on the use of mifepristone in the treatment of unresectable meningioma which are described in safety update reports received from Exelgyn as ongoing and two ongoing international studies under the sponsorship of the Population Council.

Table 1

Recently Completed/Ongoing Clinical Trials

Study Number (Country)	Indication	Number of Patients	Number of Mifepristone Patients	Study Status	Report Status (FDA Submission Status)
PC Protocols 166A & 166B (US)	Early Pregnancy Termination	2121	2121	Complete	Complete (NDA 20-687 --Amend. 024)
FFR/91/486/14-Extension (France)	Early Pregnancy Termination	970	970	Complete	4 Pg 1 this submission)
PC Protocol 172 (India)	Pregnancy Termination	907	907	In Progress	Not Available

NEW CLINICAL INFORMATION (Cont.)

Additional Extent of Patient Exposure

Patients in Clinical Trials

As stated in NDA Study Update #1, the known number of patients exposed to mifepristone in clinical trials was 28,757. This number is increased by the following patients from studies on unresectable meningioma mentioned by Exelgyn in the enclosed Periodic Safety Update Reports (PSUR) as being in progress

Study Number	Number of Patients
FFR/89/486/08	~26
USA/92/486/21	≅ 60
USA/88/486/23	28

Additionally, a total of 1,262 patients are included in the ongoing international studies sponsored by the Population Council.

The number is further increased by the completed study FFR/91/486/14-Extension which includes 970 patients to yield a total number of approximately 31,103 patients in clinical studies for various indications.

Patients in Compassionate Studies

As stated in the five PSURs from Roussel/Uclaf and Exelgyn which are included in this submission, the following estimated numbers of patients received mifepristone in "named-patient" (compassionate) studies for various indications

Periodic Safety Update Report - (PSUR) (Time Period Covered)	Number of Patients
PSUR #4 (12/1/95-5/31/96)	93
PSUR #5 (6/1/96-11/30/96)	58
PSUR #6 (12/1/96-5/31/97)	39
PSUR #7 (6/1/97-11/30/97)	71
PSUR #8 (12/1/97-8/31/98)	53

NEW CLINICAL INFORMATION (Cont.)

Additional Extent of Patient Exposure (Cont.)

Patients in Compassionate Studies (Cont.)

In the period since submission of NDA Safety Update #1, the Population Council has granted a total of 24 requests for authorization to reference ---- ---- ' in support of separate INDs from individual investigators for compassionate use of the product.

Table 2 provides a listing of the requests for authorization to reference which have been received and granted by the Population Council since the cut off date (May 15, 1996) of NDA Safety Update #1 until the end of 1998 when the responsibility for administration of the compassionate use program with mifepristone was assumed by the Feminist Majority Foundation (Arlington, VA 22209).

APPEARS THIS WAY
ON ORIGINAL

NEW CLINICAL INFORMATION (Cont.)

Additional Extent of Patient Exposure (Cont.)

Marketing Experience

In the five PSURs from Roussel Uclaf/Exelgyn which are included in this submission, it is stated that the the following estimated numbers of patients received mifepristone under marketing conditions during the periods covered by the reports

Periodic Safety Update Report - (PSUR) (Time Period Covered)	Number of Patients
PSUR #4 (12/1/95-5/31/96)	35,600
PSUR #5 (6/1/96-11/30/96)	35,700
PSUR #6 (12/1/96-5/31/97)	38,500
PSUR #7 (6/1/97-11/30/97)	37,000
PSUR #8 (12/1/97-8/31/98)	64,849

The estimates provided in the reports are based on an assumed dosage of 600 mg per patient; however, the reports caution that many physicians in the UK use a dosage of 200 mg which can lead to an underestimate of the number of patients.

In a report on ongoing pregnancies included with PSUR #8 (Page 94 of the PSUR), it is estimated by Exelgyn that approximately 400,000 patients have been treated with mifepristone since its initial marketing in France in 1989.

NEW CLINICAL INFORMATION (Cont.)

Demographics of Additional Patient Exposure

With the exception of the relatively small number of patients who have received mifepristone in clinical trials for indications other than medical termination of pregnancy or for compassionate treatment of other indications, the vast majority of additional patient exposure to mifepristone has been in international marketing. It is assumed that the demographics and characteristics of this major body of additional patients are in accord with the international prescribing information for the drug which is presented in this submission.

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources

Reports of Clinical Studies Sponsored by or Affiliated with the Population Council

Protocols 166A and 166B

Final reports on two identical clinical trials entitled "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days (Protocols 166A and 166B) were submitted to the NDA 20,687 in Amendment 024 on June 3, 1999. The studies were conducted to evaluate the safety and efficacy of mifepristone and misoprostol in the early termination of pregnancy in the US health care system and to compare the results obtained with findings from the pivotal studies submitted in NDA 20,687 which were conducted in France. The domestic studies were completed in 1995 and preliminary reports on the results were submitted to [redacted] in Submission Serial Number 185 on May 5, 1997.

No unexpected safety issues were raised in the US studies and overall safety results were regarded as similar to those observed in the pivotal French studies. After discussion with FDA that the separate presentation of results from the domestic and foreign studies in prescribing information was preferred, it was decided not to perform an integrated tabulation of results from the US studies and the French studies.

Tables 3a and 3b are adapted from the current draft prescribing information (NDA 20-687/Amendment 027 - June 25, 1999) and present the frequency of reported adverse reactions in the French and US studies.

No deaths occurred during the US studies and no patients were discontinued due to an adverse event. A subgroup of patients in the studies were administered routine clinical laboratory tests at study entry and at a follow-up evaluation. For all laboratory tests, the median changes in laboratory values were small and not of clinical significance.

Table 3a

Reported Adverse Reactions Following Administration of Mifepristone and Misoprostol In French Pivotal Studies (N=1,800)

Event	Incidence (%)* of Reports
Uterine Cramping	83
Nausea	43
Vomiting	18
Diarrhea	12
Decrease in Hemoglobin >2 g/dL	6
Pelvic Pain	2
Fainting	2
Headache	2
Dizziness	1
Asthenia	1

*Only adverse reactions with incidence >1% are included

APPEARS THIS WAY
ON ORIGINAL

Table 3b

Reported Adverse Reactions Following Administration of Mifepristone and Misoprostol In US Studies (N=859)

Event	Incidence (%)* of Reports
Abdominal Pain (Cramping)	96
Nausea	61
Headache	31
Vomiting	26
Diarrhea	20
Dizziness	12
Fatigue	10
Back Pain	9
Uterine Hemorrhage	5
Fever	4
Viral Infections	4
Vaginitis	3
Rigors (Chills/Shaking)	3
Dyspepsia	3
Insomnia	3
Asthenia	2
Leg Pain	2
Anxiety	2
Anemia	2
Leukorrhea	2
Sinusitis	2
Syncope	1

*Only adverse reactions with incidence >1% are included

APPEARS THIS WAY
ON ORIGINAL

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources (Cont.)

Reports of Clinical Studies Sponsored by or Affiliated with the Population Council (Cont.)

Protocols 172 ——— (International Studies Not Under IND ———

Protocol 172

The International Programs Division has recently completed one study in India. The objective of the study was to evaluate whether the combination of mifepristone and misoprostol for early abortion can be delivered safely through a family planning clinic and through a rural health station.

The study built on earlier work conducted through the research wings of two urban hospitals located in Bombay and in Pune and explored the feasibility of providing medical abortions to women directly through the family planning services affiliated with the hospitals. In addition, the study assessed the possibility of providing medical abortions to women in rural settings through a field hospital with surrounding community health stations in an area near Pune. In the two urban sites, 600 women with pregnancies ≤63 days since the last menstrual period were enrolled and, in the rural site, an additional 300 women with pregnancies ≤56 days participated in the study.

The study began in June 1995 and was completed in October 1998. Preliminary analysis indicates that the success rate is 93.2%. There have been no hospitalizations and no unexpected adverse events were recorded. Moreover, among the 900 women initially enrolled in the study, losses to follow-up were higher in the urban sites (3.5% in Pune and 4.4% in Bombay) than in the rural site (1.0%).

In 1998, the study protocol was modified to permit enrollment of 20 additional women in Pune with gestational ages of 63 to 70 days (as confirmed by ultrasound). The data from these 20 cases will provide preliminary information on the safety margin of 600 mg mifepristone followed two days later by 400 μg misoprostol for women with pregnancy durations of 63 to 70 days, who may inadvertently be deemed to have lower gestational ages. To date, seven women have completed this protocol. There have been no unexpected adverse events or deaths.

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources (Cont.)

Reports of Clinical Studies Sponsored by or Affiliated with the Population Council (Cont.)

Protocols 172 —— International Studies Not Under IND —— (Cont.)

Protocol 172 (Cont.)

[redacted]

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources (Cont.)

Reports of Clinical Studies Sponsored by or Affiliated with the Population Council (Cont.)

Protocols 172 —— (International Studies Not Under IND ——(Cont.)

[redacted]

Compassionate Studies

No information on safety experiences has been received by the Population Council from investigators conducting independent compassionate studies in the US and who have been authorized to reference IND —— of the Population Council.

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources (Cont.)

Information Received from Foreign Sources

Expert Report on the Clinical Documentation – Mifegyne® (mifepristone) 200 mg (August 1998)

A copy of the expert report prepared by Exelgyn in support of the 200 mg dosage form of mifepristone has been provided by that company and is presented in **Appendix 1**.

The expert report provides an overall current summary of the cumulative clinical efficacy and safety experience with mifepristone.

Report of Foreign Clinical Study (FFR/91/486/14-Extension)

The Population Council has obtained an English translation of the clinical report on an extension to the French study FFR/91/486/14 ["Efficacy and Tolerance of Mifepristone (RU 38486) at the Dose of 600 Mg in a Single Dosing in Combination with Misoprostol as an Alternative to Uterine Aspiration for Interruption of Pregnancies of an Age Lower Than or Equal To 49 Days of Amenorrhea"] which is a pivotal study in NDA 20-687. The original French version of the report on the study extension, designated as Study FFR/91/486/14-Extension, and an English translation of the summary and synopsis of the report were previously submitted to IND —— in Submission 166 on July 17, 1996. As stated in the IND submission, the results of the study are similar to those obtained in the two pivotal French studies in the NDA. The overall success rate was 94.2% and there were no unexpected serious adverse events.

A copy of the English translation of the report is provided in **Appendix 2**.

International Reports of Adverse Reactions

During the period covered by this Safety Update to the NDA, international reports of adverse reactions have been received by the Population Council in three primary formats -

NEW CLINICAL INFORMATION (Cont.)

Newly Received Woridwide Safety Information from All Sources (Cont.)

Information Received from Foreign Sources (Cont.)

International Reports of Adverse Reactions (Cont.)

- Periodic Safety Update Reports (PSUR) Numbers 4-8 covering the period from December 1, 1995 through August 31, 1998 received from Roussel Uclaf and subsequently from Exelgyn
- Two Quarterly Safety Line Listings of safety reports from clinical trials and compassionate usage of the product during the period of April 1 through September 30, 1996 when Roussel Uclaf was responsible for the product were received from that company.
- Five individual safety reports (and one follow-up report) received from Roussel Uclaf and Exelgyn for timely reporting to regulatory agencies

The PSURs provide a comprehensive summary of the safety information received by the two companies from worldwide sources during the time periods covered by the five individual reports. Some information presented in the Quarterly Safety Line Listings is from blinded studies for which the code had not been broken and in some cases the reports listed are also included in the PSURs. Similarly, the three individual safety reports (MIF0004.96GB, S970001GB/MIF1, S980006GB/MIF1) which were received by the Population Council from the French manufacturer during the time period covered by a PSUR also appear in the respective PSUR.

Individual reports of suspected adverse reactions are presented in the PSURs and quarterly listings. **Table 4** outlines the total number of new reports received in each time period covered by a PSUR and/or quarterly listing and identifies the adverse reactions which were assessed as serious. **Table 5** provides information on the individual safety reports received by the Population Council from Roussel Uclaf and Exelgyn and submitted to IND —

Copies of the five PSURs and the two quarterly listings are provided in **Appendix 3**.

Table 4

Adverse Reaction Reports Identified in Periodic Safety Update Reports #4-8* And Quarterly Line Listings

Periodic Safety Update Report (PSUR) Number/Quarterly Line Listing (Time Period Covered)	Total Number of AR Reports Received in Time Period	Reports Assessed as "Serious"			
		Reference Number	Country	Event	Unlabeled
PSUR #4 (12/01/95-05/31/96)	10	MIF0003.96GB	UK	Metrorrhagia/Incomplete Abortion	No
		MIF0003.96FR	France	Salpingitis	Yes
		MIF0004.96GB	UK	Fetal Abnormality-Acheiria/Clubfoot	Yes
		MIF0003.95GB£	UK	Fetal Abnormality-Talipes	Yes
		MIF0020.95FR/RA	France	Pulmonary Embolism	Yes
		MIF0001.96GB/RA	UK	Uterine Rupture	Yes
		MIF0002.96FR/RA	France	Pulmonary Edema/Aggravated Eclampsia	Yes
Quarterly Line Listing (04/01/96-06/30/96)	5 (4 in blinded studies)**	1996000142RU	France	Angioedema	Yes
PSUR #5 (06/01/96-11/30/96)	8	MIF0001.96SE/RA	Sweden	Petechiae/Erythematous Rash	Yes
		MIF0002.96SE/RA	Sweden	Acute Hypotensive Reaction/ Nausea/Abdominal Pain/Vagal Malaise	No
		MIF0006.96FR	France	Rash/"Baboon Syndrome" or Urticaria	No
		MIF0006.96GB£	UK	Uterine Rupture	Yes
		MIF0008.96FR/NH	France	Genital Bleeding/Loss of Consciousness/Metrorrhagia/ Incomplete Abortion	No
		199600158RU	France	Uterine Hypertonia/Fetal Heart Rate Deceleration	Yes
		199600171RU	US	Death Due to Progressive Tumor/Aggravation-Reaction	Yes

*Reports identified in Part 6 (Individual Case Histories) and Line Listings in PSURs

**Only reports from unblinded studies included in this table

Table 4 (Continued)

Adverse Reaction Reports Identified in Periodic Safety Update Reports #4-8* And Quarterly Line Listings

Periodic Safety Update Report (PSUR) Number/Quarterly Line Listing (Time Period Covered)	Total Number of AR Reports Received in Time Period	Reports Assessed as "Serious"			
		Reference Number	Country	Event	Unlabeled
Quarterly Line Listing (07/01/96-09/30/96)	4	199600284RU	US	Infection (Viral)	Yes
		199600185RU	Netherlands	Death (Compassionate Usage)	Yes
PSUR #6 (12/01/96-05/31/97)	10	MIF0001.97SE	Sweden	Heart Malformation	Yes
		MIF0002.97FR	France	Asthma/Urticaria	Yes (Asthma)
		MIF0003.96SE	Sweden	Anencephaly/Acrania/Equino-varus Bilateral	Yes (Anencephaly/ Acrania)
		MIF0009.96FR	France	Shock	Yes
		199710061RUPV	US	Pruritic Erythematous Rash	No
PSUR #7 (06/01/97-11/30/97)	17	T970001US/MIF1	US	Gastroenteritis	Yes
		S970001GB/MIF1	UK	Fetal Malformation	Yes
		S970002GB/MIF1	UK	Allergic Reaction	Yes
PSUR #8 (12/01/97-08/31/98)	13	T970002US/MIF1	US	Endometrial Hyperplasia	Yes
		S980010F/MIF1$	France	Uterus Rupture	No
		S980006GB/MIF1	UK	Disseminated Intravascular Coagulation	Yes

*Reports identified in Part 6 (Individual Case Histories) and Line Listings in PSURs

Table 5

Individual Reports of Adverse Reactions Received by the Population Council and Reported to [redacted]

IND Submission Number – Date	Reference Number	Source of Adverse Event Report	Country	Event
165-06/20/96	MIF0004.96GB	Roussel Uclaf	UK	Fetal Abnormality-Acheiria/Clubfoot
191-11/21/97	S970001GB/MIFI	Exelgyn	UK	Fetal Malformation
193-04/14/98	S980006GB/MIFI	Exelgyn	UK	Disseminated Intravascular Coagulation
198-12/17/98	S980017GB/MIFI	Exelgyn	UK	Fetal Malformation
200-02/18/99	S990001F/MIFI	Exelgyn	France	Urticaria Generalized
201-02/26/99	S980017GB/MIFI (Follow-Up)	Exelgyn	UK	Follow-up report from embryologist that association with drug is not possible

NEW CLINICAL INFORMATION (Cont.)

Newly Received Worldwide Safety Information from All Sources (Cont.)

Information Received from Foreign Sources (Cont.)

Safety Report – Birth Defects in Ongoing Pregnancies after Medical Termination with Mifepristone and Prostaglandins – Overall 10 Years Follow-Up 1987-1998 (June 8, 1998)

In the period since 1987, Roussel Uclaf and Exelgyn have received information on continuing pregnancies after administration of mifepristone or mifepristone and prostaglandins for medical termination of the pregnancies. Interim reports of this information are included in the individual PSURs and a comprehensive report and discussion on the subject is presented in PSUR #8 (**Appendix 3**). The statistics in the comprehensive report, which was prepared in June 1998, are updated through June 1999, in the supplemental information presented with the Clinical Expert Report (**Appendix 1**).

The updated information includes 87 reports of ongoing pregnancies of which 26 followed the use of mifepristone alone and the remainder followed the use of mifepristone and a prostaglandin (or unknown). Nine reports of fetal anomalies have been received; mifepristone alone was used in one report and mifepristone and gemeprost was used in eight reports.

NEW FOREIGN MARKETING INFORMATION

Mifegyne® (Mifepristone) – 200 mg

Summary of Product Characteristics
(September 1998)

Exelgyn Laboratories
6, rue Christophe Colomb
F-75008 Paris

MIFEGYNE®
200 mg
Mifepristone

Summary of Product Characteristics

September 1998

SIGN OFF PAGE
MIFEPRISTONE MASTER DATA SHEET
1998 EDITION

Head of Medicine and R & D

Name: , M.D.

Signature:

Date: October 22, 1998

Head of Regulatory Affairs

Name: Catherine BASSET, Pharmacist

Signature

Date: October 22, 1998

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

- MIFEGYNE® 200mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Mifepristone micronised .....200 mg

- Anhydrous colloidal silica .....
- Maize starch .....
- Povidone .....
- Microcrystalline cellulose .....
- Magnesium stearate.....

3. PHARMACEUTICAL FORM

- Light yellow, cylindrical, bi-convex tablets, for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Medical alternative to surgical termination of intra-uterine pregnancy.**

  In sequential use with a prostaglandin analogue, administered 36 to 48 hours after MIFEGYNE® intake (see Posology and Method of Administration):
  - misoprostol 400 µg orally (for pregnancies up to 49 days of amenorrhea),
  - or gemeprost 1 mg, vaginal pessary (for pregnancies up to 63 days of amenorrhea).

  Under these conditions, the association of mifepristone and prostaglandins leads to a success rate of about 95 per cent of the attempted pregnancy terminations.
  (See Warnings and Precautions for use)

[

]

- **Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons.**

  The use of MIFEGYNE® allows a significant reduction of the prostaglandins doses required for the expulsion.

[

]

4.2 Posology and method of administration

1) **Medical alternative to surgical termination of intra-uterine pregnancy**

MIFEGYNE® must not be administered if there is doubt as to the existence and age of the pregnancy, or in case of extra-uterine pregnancy. The prescribing doctor should in any case perform an ultrasound scan and/or measure Beta-hCG before administration.

The method of administration which will be prescribed by the physician and applied in the presence of the practitioner or of a health professional will be as follows:

- 600 mg of mifepristone (i.e. 3 tablets of 200 mg each) is taken in a single oral dose, followed by
- 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400 µg orally (pregnancies up to 49 days of amenorrhea), or gemeprost 1 mg vaginally (pregnancies up to 63 days of amenorrhea).

[

]

3) Preparation for the action of prostaglandin analogs in the termination of pregnancy for medical reasons

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single oral dose, in the presence of the physician or of a health professional, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

- Chronic adrenal failure
- Known allergy to mifepristone or to any component of the product
- Severe asthma uncontrolled by corticosteroid therapy

In the indication: medical alternative to surgical termination of intra-uterine pregnancy

- Pregnancy not confirmed by ultrasound scan or biological tests.
- Pregnancy beyond 49 days of amenorrhea with misoprostol or beyond 63 days of amenorrhea with gemeprost.
- Suspected extra-uterine pregnancy
- Contra-indications due to the prostaglandins:
  - Known allergy to prostaglandin,
  - Patients with or history of cardiovascular disease (angina, Raynaud's syndrome or disease, cardiac arrhythmias, cardiac failure, severe hypertension).
    (See Precautions for use)

Preparation for the action of prostaglandins analogues in the termination of pregnancy for medical reasons

- Contra-indications to prostaglandins where relevant.

[redacted]

4.4 Warnings and Precautions for use

Warnings

Specific national legal requirements

MIFEGYNE® and the prostaglandin analogues can only be prescribed and administered in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter by the patient would certify that she has been fully informed about the method and its risks, except in the cases of preparation to the action of prostaglandins for pregnancy termination for medical reasons as well as for the labour induction for expulsion of a dead fetus (Fetal Death in Utero).

1) Medical alternative to surgical pregnancy termination of intra-uterine pregnancy

Failures

Unless abortion has already been completed, the use of MIFEGYNE® must be followed, 36 to 48 hours later, by a prostaglandin analogue administered either vaginally or orally, as mifepristone alone given without prostaglandins would lead to a failure rate of the method of at least 20 per cent.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analogue, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (about 9 days after MIFEGYNE® intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place mandatorily within a period of **10 to 14 days** after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, Beta-hCG measurement, ultrasound scan, etc...) that expulsion has been completed and that vaginal bleeding has stopped (apart from light bleeding the disappearance of which should be checked within a few days).

Persistence of vaginal bleeding at this point could indicate incomplete abortion, or an unnoticed extra-uterine pregnancy, and an appropriate treatment should be considered.

Since heavy bleeding requiring hemostatic curettage occurs in up to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemorrhagic disorders with hypocoagulability , or with anemia.

The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anemia.

[ ]

3) Preparation for the action of prostaglandin analogs for termination of pregnancy for medical reasons

The administration of prostaglandins carries some risks; however pre-treatment with MIFEGYNE® has been shown to reduce the total dose of prostaglandins required.

[ ]

Precautions for use

1) In all instances

- The use of MIFEGYNE® requires blood group and rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any pregnancy termination.

- In case of suspected acute adrenal failure, dexamethasone administration is recommended.

- Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE® 's intake. Therapy should be adjusted.

  In the event of inhaled corticosteroid therapy, particularly in patients with asthma, it is recommended to adjust the treatment by doubling the dose during the 48 hours preceding mifepristone's administration and for about one week duration.

- In patients with Insulin-dependent Diabetes, the occurrence of gastro-intestinal disorders induced by the pregnancy itself or by the treatment, would require an adjustment of insulin therapy.

- During clinical trials, pregnancies occurred between fetal expulsion and the resumption of menses: in order to prevent the occurrence of another unwanted pregnancy, it is therefore recommended that a contraceptive method is prescribed as early as possible.

- As a precaution and in the absence of specific studies, mifepristone should not be used in patients with:
  - Renal failure
  - Liver failure
  - Malnutrition

2) **Medical alternative to surgical termination of intra-uterine pregnancy**

In any case of a pregnancy occurring on a intra-uterine device, this device must be removed before administration of MIFEGYNE®.

During the initial clinical trials, rare serious cardiovascular accidents similar to coronary spasm have been reported following the administration of a PGE_2 analogue (intra-muscular sulprostone). These events were reported in women over 30 years of age and smoking more than 10 cigarettes a day.

No such cases have been reported, since analogues of PEG_1 (gemeprost or misoprostol) have been used. The present experience is based upon 400,000 treatments of which about 320,000 used misoprostol and about 80,000 used gemeprost.

Therefore, as a special precaution, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

In any case, the risk of cardiovascular events must be taken into consideration when prostaglandins are used in association with mifepristone.

Method of prostaglandins administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be fitted with the appropriate cardiovascular monitoring and resuscitation equipment.

3) **For the sequential use of MIFEGYNE® - Prostaglandins, whatever the indication**

The precautions related to the prostaglandins used should be followed where relevant.

4.5 Interaction with other drugs and other types of interactions.

Associations to be avoided

- Non steroidal anti-inflammatory drugs (NSAIDs) including aspirin. A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of NSAIDs. Use preferably non-NSAIDs analgesics.

4.6 Pregnancy and lactation

Patients must be informed that in the event of failure of the methods, the pregnancy is liable to continue to develop. The fetus may then be exposed to a risk of malformation.

In studies performed in animals, fetal anomalies have been observed in rabbits (skull lesions), but not in rats and mice. No teratogenicity was observed after in vitro exposure of monkey embryos to mifepristone. When the pregnancy continued after mifepristone alone or with prostaglandins, uncommon cases of malformations have been reported in the fetus or the infant. Malformations have also been reported after the use of prostaglandins alone.

The exact role of mifepristone, prostaglandin analogue, or coincidental event cannot be established.

It is essential that termination of pregnancy by another method be undertaken at a follow-up visit, in the event of such failure.

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no pharmacokinetic data is available in those conditions. It is recommended that breast feeding is interrupted for 3 or 4 days after mifepristone is administered.

4.7 Effects or ability to drive and to use machines

4.8 Undesirable effects

Very common	>1/10		
Common	>1/100	and	<1/10
Uncommon	>1/1000	and	<1/100
Rare	>1/10,000	and	<1/1000
Very rare	<1/10,000		