

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-687

CHEMISTRY REVIEW(S)

/S/

JUN 20 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA: 20-687
CHEMISTRY REVIEW # 1

DATE REVIEWED: 20 June 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	14 Mar. 1996	19 Mar. 1996	20 Mar. 1996
AMENDMENTS	19 Apr. 1996	22 Apr. 1996	

NAME & ADDRESS OF APPLICANT: The Population Council
1230 York Avenue
New York, NY 10021

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/Established/USAN: Mifepristone Tablets
Code Name/#: RU 486
Chem. Type/Ther. Class: 1P

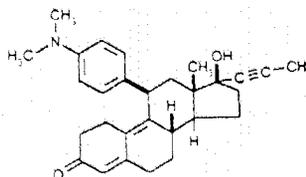
PHARMACOLOGICAL CATEGORY/INDICATION: Antiprogestational and antiglucocorticoid agent for the induction of abortion

DOSAGE FORM: Tablets
STRENGTHS: 200 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

11 β -(4-Dimethylaminophenyl)-17 β -hydroxy-17 α -(1-propynyl)-estra-4,9-dien-3-one

C₂₉H₃₅NO₂
Mol. Wt. 429.58



SUPPORTING DOCUMENTS:

IND
IND

RELATED DOCUMENTS: N/A

CONSULTS: EER sent on 17 April 1996; EA.

REMARKS/COMMENTS: To preserve confidentiality of the information, the CMC section of this NDA has been submitted directly by the manufacturer as an Amendment, dated 27 Oct. 1995, to IND [redacted]. This information has been reviewed and the deficiencies identified will be conveyed to the Applicant. Review of the Environmental Assessment Report, submitted to IND [redacted] as an Amendment dated 8 Mar. 1996, for this new molecular entity is the responsibility of [redacted] of [redacted]. The EER was returned on 15 May 1996 with an acceptable cGMP status.

CONCLUSIONS & RECOMMENDATIONS: NDA 20-687 may be approved from a chemistry, manufacturing and controls viewpoint after a satisfactory response, in the form of an Amendment, is received from the Applicant to the deficiencies identified in the draft letter in Chemistry Review # 1 (13 June 1996) of IND [redacted]. Minor labeling changes may also be needed.

[redacted] /S/

[redacted]

cc:

Org. NDA 20-687

[redacted]

R/D Init by:

[redacted] /S/

6/20/96

[redacted]

APPEARS THIS WAY
ON ORIGINAL

JAN 11 1999

/S/

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #:20-687
CHEMISTRY REVIEW #: 2

DATE REVIEWED: 28-DEC-1998
REVIEWER: [redacted]

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	14-MAR-1996	19-MAR-1996	20-MAR-1996
AMENDMENT	05-AUG-1997		
AMENDMENT	24-SEP-1997	29-SEP-1997	

NAME & ADDRESS OF APPLICANT:

The Population Council
1230 York Avenue
New York, NY 10021

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name/#:
Chem.Type/Ther.Class:

Mifepristone tablets
RU 486
1P

PHARMACOL. CATEGORY/INDICATION:
for the induction of labor

Antiprogestational and antiglucocorticoid agent

DOSAGE FORM:

Tablet

STRENGTHS:

200 mg

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one

Molecular fomula: C₂₉H₃₅NO₂

Molecular weight: 429.58

See Chemistry Review #1 for NDA 20-687 (6/20/96) for structural formula.

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND [redacted]	Mifepristone	Population Council	Open	6/13/96	N/A

RELATED DOCUMENTS: N/A

CONSULTS: See Chemistry Review #1 (20-JUN-96).

REMARKS:

These amendments contain CMC information on the Gedeon Richter synthesis of mifepristone. The sponsor would like to designate the pilot scale batches synthesized by Gedeon Richter as a reference standard. This would be in addition to the current reference standard synthesized by Roussel. An inspection of the Gedeon Richter facilities has not been conducted and final approval of the Gedeon Richter drug substance cannot be provided until there is an acceptable cGMP status.

CONCLUSIONS & RECOMMENDATIONS:

The drug substance in NDA 20-687 may be approved from a chemistry, manufacturing and controls point of view after satisfactory response to the issues delineated in the draft letter. In addition, the Gedeon Richter facilities must have an acceptable cGMP status, if the drug product is to be used in any clinical studies, including compassionate use.

[Redacted] /S/ 1/9/99
[Redacted]

cc:
Org. NDA 20-687

[Redacted]
R/D Init by: [Redacted] 151 11/11/99
[Redacted]

APPEARS THIS WAY
ON ORIGINAL

DEC 10 1999

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #:20-687

DATE REVIEWED: 02-DEC-1999

Revised: 10-DEC-1999

CHEMISTRY REVIEW #: 3

REVIEWER: [REDACTED]

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>
ORIGINAL	14-MAR-1996
AMENDMENT	18-AUG-1999

<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
19-MAR-1996	20-MAR-1996
19-AUG-1999	20-AUG-1999

see list of other amendments on page 3.

NAME & ADDRESS OF APPLICANT:

The Population Council
1230 York Avenue
New York, NY 10021

DRUG PRODUCT NAME

Proprietary:

Established:

Code Name/#:

Chem.Type/Ther.Class:

Mifeprex tablets (tradename consult pending)
Mifepristone
RU 486
1P

PHARMACOL. CATEGORY/INDICATION:

for the induction of labor

Antiprogestational and antiglucocorticoid agent

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

Rx/OTC:

SPECIAL PRODUCTS:

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

Tablet

200 mg

Oral

Rx OTC

Yes No

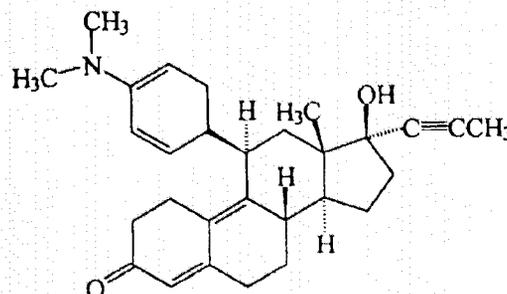
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

11β-[(p-Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

Molecular fomula: C₂₉H₃₅NO₂

Molecular weight: 429.60

CAS # 84371-65-3



BEST POSSIBLE COPY

NDA 20-687

Sponsor: Population Council

Drug: Mifeprex Tablets
(mifepristone)

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND [redacted]	Mifepristone	Population Council	Open	6/13/96	N/A
DMF [redacted]	Rigid PVC film for blister, [redacted] (opaque)	[redacted]	Adequate	2/25/99	N/A
DMF [redacted]	Aluminum foil [redacted]	[redacted]	Pending		

RELATED DOCUMENTS: IND [redacted]

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications and review of equivalence data between the tablets manufactured by [redacted] RU.
2. The EER was sent to Compliance on September 1, 1999. The final recommendation is pending (see appendix A).
3. The proposed tradenames, MIFEPREX (1st choice) and [redacted] was sent to the Nomenclature and Labeling Committee on November 5, 1999 and then to OPDRA on November 10, 1999. The review is pending.

REMARKS:

The series of amendments submitted by the sponsor is in response the September 18, 1996 FDA Approvable Letter. These amendments contain CMC information on the [redacted] synthesis of mifepristone and the manufacture of the drug product tablets by [redacted]. These [redacted] contract manufacturers are to replace the original manufacturers, Gedeon Richter and Rousell Uclaf (RU). The sponsor states that the synthetic process for the bulk drug substance and the manufacturing process for the drug product tablets are the same as conducted by RU. The sponsor would like to designate the batches synthesized by [redacted] as a reference standard. This would replace the current reference standard synthesized by RU.

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-687 may be approved from a chemistry, manufacturing and controls point of view after satisfactory response to the issues delineated in the draft letter. In addition, the [redacted] facilities listed for this NDA must have an acceptable cGMP status.

cc:

Org. NDA 20-687

R/D Init by: [redacted] 12/10/99

[redacted] /S/

[redacted] 12/10/99

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #:20-687

DATE REVIEWED: 08-FEB-2000

Revised: 11-FEB-2000

CHEMISTRY REVIEW #: 4

REVIEWER: [redacted]

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	14-MAR-1996	19-MAR-1996	20-MAR-1996
Amendment	28-JAN-2000	31-JAN-2000	02-FEB-2000

NAME & ADDRESS OF APPLICANT:

The Population Council
1230 York Avenue
New York, NY 10021

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name/#:
Chem.Type/Ther.Class:

[redacted] tablets
Mifepristone
RU 486
1P

PHARMACOL. CATEGORY/INDICATION:

for the induction of labor

Antiprogestational and antiglucocorticoid agent

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

Rx/OTC:

SPECIAL PRODUCTS:

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

Tablet
200 mg
Oral
 Rx OTC
 Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

11β-[(p-Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

see Chemistry Review # 3 for structure

Molecular fomula: C₂₉H₃₅NO₂

Molecular weight: 429.60

CAS # 84371-65-3

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND [redacted]	Mifepristone	Population Council	Open	6/13/96	N/A
DMF [redacted]	Rigid PVC film for blister, [redacted] (opaque)	[redacted]	Adequate	2/25/99	N/A

DMF [redacted]	Aluminum foil [redacted]	[redacted]	Adequate	2/10/00	N/A
----------------	--------------------------	------------	----------	---------	-----

RELATED DOCUMENTS: IND [redacted]

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications and review of equivalence data between the tablets manufactured by [redacted] and RU (see Appendix A for recommendation).
2. The EER was sent to Compliance on September 1, 1999. The Office of Compliance issued an overall withhold recommendation on December 20, 1999 (see appendix B).
3. The proposed tradenames, MIFEPREX (1st choice) and [redacted] were sent to the Nomenclature and Labeling Committee on November 5, 1999 and then to OPDRA on November 10, 1999. OPDRA determined that the use of [redacted] would be acceptable (see Appendix C).
4. [redacted] from the Office of Compliance was consulted concerning the labeling for the shipping cartons (see Appendix D).

REMARKS:

The January 28, 2000 amendment (#040) contains the sponsor's responses to the issues delineated in the December 14, 1999 Agency Information Request Letter. This IR letter was generated after review of the sponsor's complete response to the September 18, 1996 Approvable Letter (see Chemistry Review #3).

All the CMC issues in the September 18, 1996 Approvable Letter have been adequately addressed except for Point #1 from page 1 and Point #2 from page 9.

The comments in the draft letter for Chemistry Review #2 pertained to Gideon Richter as the drug substance manufacturer and are no longer relevant because the drug substance manufacturer is now [redacted]

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-687 may be approved from a chemistry, manufacturing and controls point of view after satisfactory response to the issues delineated in the draft letter. In addition, the two facilities listed for this NDA must have an acceptable cGMP status.

cc:
Org. NDA 20-687

[redacted]
[redacted]
[redacted]

R/D Init by:

[redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

/S/

AUG 29 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #:20-687
CHEMISTRY REVIEW #: 5

DATE REVIEWED: 29-AUG-2000
REVIEWER: _____

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	14-MAR-1996	19-MAR-1996	20-MAR-1996
Amendment	30-MAR-2000	31-MAR-2000	31-MAR-2000
Amendment	20-APR-2000	21-APR-2000	
Amendment	03-MAY-2000	04-MAY-2000	
Amendment	11-MAY-2000	12-MAY-2000	
Amendment	17-MAY-2000	18-MAY-2000	
Amendment	22-JUN-2000	23-JUN-2000	
Amendment	13-JUL-2000	14-JUL-2000	
Amendment	25-JUL-2000	26-JUL-2000	
Amendment	21-AUG-2000	22-AUG-2000	
Amendment	24-AUG-2000	25-AUG-2000	

NAME & ADDRESS OF APPLICANT:

The Population Council
1230 York Avenue
New York, NY 10021

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name/#:
Chem.Type/Ther.Class:

Mifeprex Tablets
Mifepristone
RU 486
1P

PHARMACOL. CATEGORY/INDICATION:

for the induction of labor

Antiprogestational and antiglucocorticoid agent

DOSAGE FORM:

Tablet

STRENGTHS:

200 mg

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

11β-[(p-Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

see Chemistry Review # 3 for structure
Molecular fomula: C₂₉H₃₅NO₂
Molecular weight: 429.60
CAS # 84371-65-3

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND [redacted]	Mifepristone	Population Council	Active	6/13/96	N/A
DMF [redacted]	Rigid PVC film for blister, [redacted] (opaque)	[redacted]	Adequate Reviewed by [redacted]	2/25/99	N/A
DMF [redacted]	Aluminum foil [redacted]	[redacted]	Adequate Reviewed by this reviewer	2/10/00	N/A

RELATED DOCUMENTS: IND [redacted]**CONSULTS:**

1. The EER was sent to the Office of Compliance on March 3, 2000. The Office of Compliance issued a final acceptable recommendation on August 25, 2000 (see Appendix A).
2. OPDRA has been reviewed the proposed proprietary name, Mifeprex, and determined it to be unacceptable (see Chemistry Review #4 dated 2/11/00). However, the Office of Drug Evaluation 3 (ODE 3) has determined that Mifeprex is acceptable (see Office Director's memo).

REMARKS:

The March 30, 2000 amendment (#043) contains the sponsor's complete response to the deficiencies delineated in the February 18, 2000 Agency Approvable Letter.

The April 20, 2000 (#044) amendment contains updated drug product stability data, in response to Approvable Letter.

The May 3, 2000 amendment (#045) contains three copies of the complete updated Methods Validation Package, in response to Approvable Letter.

The May 11, 2000 amendment (#046) contains the Certificate of Analysis for the drug substance reference standard, in response to Approvable Letter.

The May 17, 2000 amendment (#047) contains: 1) commitment to develop [redacted] 2) impurities data to link stability data of Roussel drug product to Danco drug product, and 3) revised stability commitment, in response to Approvable Letter.

The June 22, 2000 amendment (#048) contains a description of the drug substance manufacturing process changes implemented after the validation batches described in Chemistry Review #3. This is new information.

The July 13, 2000 amendment (#052) contains drug substance characterization data to support the process changes described in the June 22, 2000 amendment. This is new information.

NDA 20-687

Sponsor: Population Council

Drug: Mifeprex Tablets
(mifepristone)

The July 25, 2000 (#053) amendment contains updated drug product stability data, a revised stability commitment, and a mock-up sample of the primary and secondary package.

The August 21, 2000 amendment (#55) contains in-vitro dissolution comparison of drug product batches containing pre-process change drug substance and post-process change drug substance. In addition, updated stability data have been provided for post-process change drug substance.

The August 24, 2000 amendment (#56) contains an updated final product specifications, which reflects the removal of the [redacted] method.

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-687 may be approved from a chemistry, manufacturing and controls point of view.

[redacted] /S/ [redacted]
[redacted]

8/29/00

cc:

Org. NDA 20-687

[redacted]

R/D Init by:

[redacted]

/S/ 8/29/00

APPEARS THIS WAY
ON ORIGINAL