CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-687

MIFEPRISTONE TABLETS

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS (HFD-580)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-687

Mifepristone Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research (CDER) has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Mifepristone Tablets, The Population Council** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Mifepristone is a synthetic drug which will be administered orally to provide a medical approach to the termination of early pregnancy. Mifepristone may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA in accordance with CDER guidance.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste will be disposed of by the manufacturer and The Population Council at licensed disposal facilities. At U.S. hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to standard procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

7/9/96
DATE

/S/
PREPARED BY

7/11/96
DATE

/S/
CONCURRED

Center for Drug Evaluation and Research

Attachment: Environmental Assessment

APPEARS THIS WAY
ON ORIGINAL

1. DATE

March 1, 1996

2. NAME of APPLICANT

The Population Council

3. ADDRESS

1230 York Avenue
New York, NY 10021

4. DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Applicant seeks approval for mifepristone tablets, (200 mg/tablet), packaged in a 200 μm white opaque poly (vinyl chloride-aceto chloride) blister with a 20 um aluminum foil with heat sealable varnish.

b. Need for Action

Mifepristone is a synthetic norsteroid which has demonstrated activity as a potent antagonist for progestins and glucocorticoids, due to its high relative binding to the progestorone and glucocorticoid receptor.
Progesterone is a critical hormone in mammalian reproduction and is essential for the maintenance of pregnancy. Withdrawl of the influence of progesterone in the uterus due to its competitive inhibition by mifepristone at the receptor site results in uterine bleeding, disruption of the placental function and disruption of the inhibitory effects of progesterone on the myometrial stimulatory actions of prostaglandins. These antiprogestational activities of the compound serve to provide a medical approach to the termination of early pregnancy.

c. Production Location

To perserve confidentiality of proprietary information, the name and location of the third-party manufacturer of

mifepristone drug substance and drug product is contained in confidential Appendix A.

d. Locations of Use

The drug product will be used by women in the United States. It will be administered in hospitals, health clinics and private physicians' offices.

e. Disposal Sites

Rejected, expired, returned or waste drug products are expected to be disposed of in accordance with the Center for Disease Control Guidelines for the handling of hazardous waste in the clinic or healthcare provider's office.

Rejected, expired or waste drug products will be collected and sent to a licensed facility to be processed and incinerated or for grinding and landfill. The facility and the permit/license under which it operates is identified in confidential Appendix B.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

a. Nomenclature

i. Established Name

Mifepristone

ii. Brand/Proprietary Names

Tradename in US not established
Mifegyne® (tradename used in European countries)
Xi Bai Lu (tradename used in China)

iii. Chemical Names

Chemical Abstracts:
(11beta,17beta)-11-[(4-dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one

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

iv. Laboratory Code Designations

RU 38 486
RU 486

b. Chemical Abstracts Service (CAS) Registration Number

84371-65-3

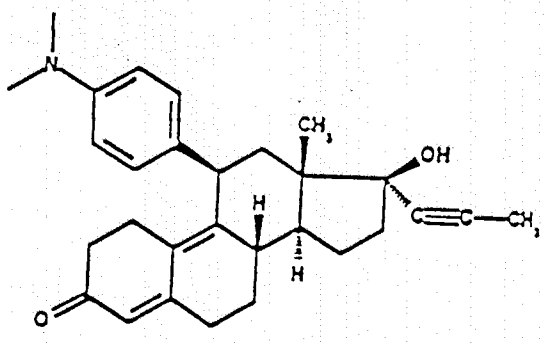
c. Molecular Formula

$C_{29}H_{35}NO_2$

d. Molecular Weight

429.58

e. Structural Formula



f. Physical Description

Mifepristone is a light yellow to yellow crystalline powder. The melting point is 191 - 196° C.

g. Additives

The dosage form is a pale yellow, cylindrical biconvex tablet, 11 ml in diameter. Each 350 mg tablet contains:

mifepristone: 200 mg
colloidal silica anhydrous: 3 mg
maize starch: 102 mg
povidone: 12 mg
cellulose microcrystalline: 30 mg
magnesium stearate: 3 mg

h. Impurities

The drug substance specifications, including impurities is included in confidential Appendix C.
No impurities are greater than 1%.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Items a - d are covered in the information included in confidential Appendix A.

The Material Safety Data Sheet (MSDS) is included in nonconfidential Appendix D.

e. Expected Introduction Concentrations

i. Expected Introduction Concentration from Use

The expected environmental concentration was calculated using the following equation:

EIC-Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liters per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

* 1.115×10^{11} liters per day entering publicly owned treatment works (POTW's), Source: 1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002

The actual calculations are considered confidential business information and are provided in confidential Appendix E.

The expected concentration is less than 1 ppb, which normally relieves the applicant from providing information in format items 7 - 11 and 15 in accordance with the Tier 0 approach described in the FDA's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements* (November 1995).

7 - 11. Not provided, based on the Tier 0 approach described in FDA's *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements* (November 1995).

12. LIST OF PREPARERS

Ann Robbins, Ph.D
Scientist

The names of prepares from the third party manufacturer are contained in confidential Appendix A.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the Population Council.

The undersigned official certifies that the EA summary document and Appendix ~~E~~ D EDA 6/21/96 contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CRF 1506.6

Date Mar 1 1996

Signature Ann Robbins

Ann Robbins, Ph.D
Scientist
The Population Council
Center for Biomedical Research

The certification from the third-party manufacturer is included in confidential Appendix A.

14. REFERENCES

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Appliations and Supplements, Center for Drug Evaluation and Research (CDER), FDA, November 1995.

APPENDICES

Appendix A: (CONFIDENTIAL) Information on third party manufacturer
Appendix B: (CONFIDENTIAL) Name and location of licensed disposal site
Appendix C: (CONFIDENTIAL) Drug substance specifications
Appendix D: Material Safety Data Sheet (MSDS)
Appendix E: (CONFIDENTIAL) Expected introduction concentration calculations

APPENDIX D

MATERIAL SAFETY
DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION

IDENTIFICATION OF THE SUBSTANCE OR PREPARATION

TRADE NAME	: MIFEPRISTONE
CHEMICAL FAMILY	: Hormone
FORMULA	: C29H35NO2
MOLECULAR MASS	: 429
KIND OF USE	: Medical use

2. COMPOSITION/INFORMATION ON INGREDIENTS

SUBSTANCE

CAS NUMBER	: 84371-65-3
CHEMICAL NAME	: 17beta-hydroxy-11beta-(4-dimethylaminophenyl)17-alpha-(pro 1-ynyl)estra 4,9-dien 3-one.

3. HAZARDS IDENTIFICATION

MAIN HAZARDS : TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

4. FIRST-AID MEASURES IN CASE OF EXPOSURE

INHALATION	: Make the victim blow his nose Make victim breathe fresh air
SKIN CONTACT	: Rinse with plenty of water
EYES CONTACT	: Rinse immediately with plenty of water for at least 15 minutes
INGESTION	: Alert a physician

5. FIRE-FIGHTING MEASURES

SUITABLE EXTINGUISHING MEDIA	: Usual means .
UNSUITABLE EXTINGUISHING MEDIA	: None.

FIRE AND EXPLOSION HAZARDS	: In case of fire, the product emits toxic and irritating fumes .
SPECIAL PROTECTIVE EQUIPMENT	: Wear a self-contained respiratory apparatus.
OTHER RECOMMENDATIONS	: None.

6. ACCIDENTAL RELEASE MEASURES

MEASURES AFTER LEAKING OR SPIL	: Collect thouroughly into plastic bag. Avoid dust emissions. Rinse the polluted area with plenty of water.

7. HANDLING AND STORAGE

HANDLING

TECHNICAL MEASURES	: Mechanical sucking ventilation at source of formation of dust.
SPECIAL PROTECTION MEASURES	: Have a shower after handling.

STORAGE

SENSITIVITY TO DAMP	: Not observed.
SENSITIVITY TO LIGHT	: Not observed.
SENSITIVITY TO OXIDATION	: Sensitive to air
SPECIAL STORAGE REQUIREMENTS	: Room temperature (<86 F)
STORAGE CONDITIONS	: Usual conditions (T <= 86 F, away from light)
SHELF LIFE	: 5 years.
STORAGE FACILITIES	: Toxic products.
INCOMPATIBLE SUBSTANCES	: None.
RECOMMENDED PACKAGING MATERIAL	: Glass, polythene.
SUPPLIER PACKAGING	: polythene bag.
PACKAGING MATERIAL TO BE AVOIDED	: Unknown.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

CONTROL OF EXPOSURE

TWA	: ND
STEL	: ND
IDLH	: ND
OLFACTORY THRESHOLD	: ND

PERSONAL PROTECTION/WORKSHOP

RESPIRATORY TRACT PROTECTION	: Wear a dust respirator.
PROTECTIVE GLOVES	: Wear suitable gloves
EYES PROTECTION	: Wear glasses
OTHER EQUIPMENT PROTECTION	: Complete overall, skullcap

PERSONAL PROTECTION/LABORATORY

RESPIRATORY TRACT PROTECTION	: Wear a dust respirator.
PROTECTIVE GLOVES	: Wear suitable gloves
EYES PROTECTION	: Wear glasses

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE	: Crystallized solid,(yellow)

pH	: Not applicable.
CHARACTERISTIC TEMPERATURES	: Melting point : 192-196°C
FLASH POINT	: Not applicable.
AUTOINFLAMMABILITY	: Not determined.
EXPLOSIVITY CHARACTERISTICS	: NA
COMMENTS ON FLAMMABILITY	: Not concerned.
VAPOUR PRESSURE	: Not determined.
VOLUMIC MASS	: Not determined.
SOLUBILITY	: Insoluble in water Soluble in : alcohol,ether,chloroform.
OTHER DATA	: alpha D : + 143° (1%,chloroform). alpha D : + 125°(0.5%, methylene chloride)

10. STABILITY AND REACTIVITY

HAZARDOUS REACTIONS	: Unknown.
HAZARDOUS DECOMPOSITION PRODUCTS	: Unknown.

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY	: LD 50 oral route/rat : > 5000 mg/kg. LD50 oral/route in dogs : > 5000 mg/kg.
PHYSIOLOGICAL ACTIVITY	: Substance physiologically very active., : anti-progestative, abortive.
SPECIFIC EFFECTS	: Teratogenicity : embryolethal in rat, mice, rabbit per oral route. Not teratogenic in surviving rat and mice foetuses. Teratogenic effects have been seen in rabbit foetuse (undirect action, at low frequency). Mutagenicity : not mutagenic.
COMMENTS/SYMPTOMS	: TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
OTHER RECOMMENDATIONS	: Handling inadvisable for pregnant women Possibly, seek medical advice

12. ECOLOGICAL INFORMATION

ENVIRONMENT	: Biodegradable in natural media

13. DISPOSAL CONSIDERATIONS

NEUTRALIZATION OF THE PRODUCT	: Set in specialized and approved recuperator service
DESTRUCTION SOILED PACKAGING	: Empty and rinse well.

14. TRANSPORT INFORMATION

INTERNATIONAL REGULATIONS

LAND WAYS	: 6.1,90°b,6.1
MARITIME WAYS	: 6.1,gr II,p6236.6 poison
AERIAL WAYS	: 6.1,gr II,,6 poison
CARGO	: 615 (100 kg)
PASSENGERS	: 613 (25 kg)
ONU	: 2811

OTHER REGULATIONS

LAND WAYS - FRANCE : 6.1,90°b,6.1

SPECIAL PRECAUTIONS

15. REGULATORY INFORMATION

COMMUNITY REGULATIONS

LABELLING (EEC NUMBER)	: Labelling according to EEC regulations
SYMBOLS	: T
PHRASES	: (B) R23/24/25 S36/37/39-S15
SPECIAL RISKS	: TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
SAFETY ADVICES	: Wear suitable protective clothing, gloves and eye/ face protection. Keep away from heat.
ADDITIONAL LABELLING	: Room temperature (<86 F)

16. OTHER INFORMATION

FURTHER INFORMATIONS : None.

All the regulatory instructions mentioned are intended to help the addressee to comply with his obligations when using the product.This list cannot be considered as exhaustive and does not discharge the addressee from his duty to enquire about all other regulatory provisions which may apply to the posession and handling of the product for which he bears sole liability.

The information given in this data sheet has been introduced in accordance with the guidelines established by article 10 of EEC directive, dated March 5, 1991.
This data sheet complements the user's instructions, but does not replace them.
The information it contains is based on the knowledge available about the product concerned at the time it was compiled. Users are further reminded of the possible risks of using a product for purposes other than those for which it was intended.
The required information complies with current EEC legislation; addressees are requested to apply any additional national requirements.

/S/

JUL 22 1996

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-687

MIFEPRISTONE

TABLETS

DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS (HFD-580)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: July 9, 1996

SUMMARY

A FONSI is recommended.

Precautions taken at the sites of manufacture and the disposal methods are expected to minimize occupational exposures and environmental release.

A Tier 0 EA was submitted in accordance with the Industry Guidance. The production estimate is [redacted] kg which is equivalent to an EIC of [redacted] ppb. There is no information that indicates extraordinary circumstances exist that would warrant the submission of additional environmental information.

ENVIRONMENTAL ASSESSMENT

1. **Date:**

EA dated: 03/01/1996
Consult #1: 03/20/1996

2. **Name of applicant/petitioner:**

The Population Council

ADEQUATE

3. **Address:**

1230 York Avenue
New York, NY 10021

ADEQUATE

4. **Description of the proposed action:**

a. **Requested Approval:**

The applicant is requesting approval of the product--200 mg mifepristone tablets. A brief description of the product packaging is provided. The product will be in packaging that is commonly used.

ADEQUATE

b. **Need for Action:**

Used in the termination of early pregnancy.

ADEQUATE

c. **Production Locations:**

i. **Proprietary Intermediate(s):**

The chemist confirmed that there are no proprietary intermediates manufactured elsewhere.

ADEQUATE

ii. **Drug Substance:**

ROUSSEL UCLAF
Vertolaye Plant
63480 Vertolaye
France

ADEQUATE

iii. **Finished Dosage Form:**

ROUSSEL UCLAF
USIPHAR Plant
Route de Choisy-au-Bac
60205 Compiegne
France

ADEQUATE

Facility Description & Adjacent Environment:
A brief description has been provided for each of the facilities. **ADEQUATE**

Note: The information for both of these production facilities is classified as confidential. [redacted] the review chemist, was consulted as to what companies were identified on the labeling. The labeling only identifies The Population Council as the distributor, therefore these facilities can be confidential.

d. **Expected Locations of Use (Drug Product):**

The drug will be used by women in the United States. It will be administered in hospitals, health clinics and physicians' offices. **ADEQUATE**

e. **Disposal Locations:**

Disposition of rejected, expired, returned or waste drug products are expected to disposed of:

1. "In accordance with the Center for Disease Control [sic] Guidelines for handling of hazardous waste in the clinic or healthcare provider's office";

2. The applicant will use a licensed incineration or grinding and landfill facility to dispose of this type of material.

The applicant is in the process of identifying a licensed disposal site to dispose of this product. In the past FONSI's have been written for EAs with identification of the disposal facility as long as it was indicated that a licensed facility would be used. Lack of this information is not considered sufficient to delay issuance of a FONSI. **ADEQUATE**

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: Mifepristone

Chemical Name: Chemical Abstracts
(11beta, 17beta)-11-[(4-dimethylamino) phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-diene-3-one

IUPAC
11-beta-4-dimethylaminophenyl-17beta-17α-(1-propynyl-estra-4,9-diene-3-one

CAS #: 84371-65-3

Molecular Weight: 429.58

Molecular Formula: $C_{29}H_{35}NO_2$

Structural Formula: Provided on page 3.

Physical Descrip.: Light yellow to yellow crystalline powder

Additives: The excipients used in the drug product are provided.

Impurities: They state that there are no impurities greater than [redacted]. The Industry Guidance indicates that identification is not necessary in this case.

ADEQUATE

6. **Introduction of substances into the environment: For the site(s) of production:**

a. **Substances Expected to be emitted:**

The chemicals expected to be emitted from drug substance manufacture are include on pages 75-78. The composition of the drug product is included in the non-confidential EA. **ADEQUATE**

b. Controls (Air, Liquid Effluent, Solid):

Drug substance:
In the table listing the emitted substances there is a discussion of the depollution treatment for each waste stream. In general, air emissions are filtered, pre-treated aqueous waste streams are subjected to biological treatment, some solvents are incinerated or recovered and solid waste is sent to off-site disposal facilities in accordance with French regulations.

Drug product:
In general, air emissions are filtered, pre-treated aqueous waste streams are subjected to biological treatment, solvents are incinerated and solid waste is either incinerated or in the case of packaging material recycled.

ADEQUATE

c. Compliance with Federal, State and Local Emission Requirements:

Although there is no specific statement regarding compliance, the manufacturer states that their facilities "operate with all technical means required to protect, preserve and enhance the quality of the environment as specified by French Law in the fields of environmental protection and occupational hygiene." Various French laws and requirements are cited throughout the document. English translations of French government reports are also included as supporting information (originals not provided).
ADEQUATE

d. Effect of Approval on Compliance with Current Emissions Requirements:

It is stated that approval will have no adverse effect upon compliance with current emission requirements.
ADEQUATE

e. Estimated Expected Emitted Concentration/Quantities:

The production estimate is [redacted] kg which is equivalent to an EIC of [redacted] ppm ([redacted] ppb, [redacted] pptr). These calculations do not consider metabolism.
ADEQUATE

7. **Fate of emitted substances in the environment:**
8. **Environmental effects of released substances:**
9. **Use of resources and energy:**
10. **Mitigation measures:**
11. **Alternatives to the proposed action:**

Format items 7-11 are not normally necessary if the EIC is < ppb (See "Tier 0" Industry Guidance). The EIC is much less than ppb even without consideration of metabolism. There are no extraordinary circumstances that indicate additional environmental information is warranted. **ADEQUATE**

12. **List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:**

The preparers are identified along with their titles/experience. **ADEQUATE**

13. **Certification:**

The certification is acceptable except Appendix E is listed as non-confidential which contradicts the listing in format item 15. I spoke to Ann Robbins of The Population Council on 7/9/96 and she confirmed that Appendix D is the non-confidential appendix. This will be corrected by hand. **ADEQUATE**

14. **References:**

References are provided. **ADEQUATE**

15. **Appendices:**

Five appendices are attached, four are designated as confidential. **ADEQUATE.**

The EA is formatted appropriately for public release.

Endorsements:

[redacted] /S/ 7/9/96

[redacted] /S/ 7/11/96

CC: Original to NDA 20-687/through [redacted]
EA File 20687

[redacted]

APPEARS THIS WAY
ON ORIGINAL