| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION | DISTRICT ADDRESS AND PHONE NUMBER<br>U.S. Food & Drug Administration, CDER, HFD-322<br>Div. of Manufacturing & Product Quality, FIT<br>7520 Standish Place Rockville, MD 20855. U.S.A.<br>Phone: 001 ——— FAX 001 ——— |
|---|---|
| NAME OF INDIVIDUAL TO WHOM REPORT ISSUED<br>TO: Mr. Li Changfa | PERIOD OF INSPECTION: 10/25-28/99 — C. F. NUMBER: 96-15606 |
| TITLE OF INDIVIDUAL<br>Chairman | TYPE ESTABLISHMENT INSPECTED<br>API Manufacturer |
| Shanghai Hua Lian Pharmaceutical Co., Ltd. – XinLian Pharmceutical Factory | NAME OF FIRM, BRANCH OR UNIT INSPECTED<br>Same |
| STREET ADDRESS<br>217 Ming Le Road | STREET ADDRESS OF PREMISES INSPECTED<br>Same |
| CITY AND STATE (Zip Code)<br>Shanghai 201419, China | CITY AND STATE (Zip Code)<br>Same |

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

c) — reaction, CMC 143, section 2.1.3 states that the method is ———. Although a ——— ; run, the former — method is being used for evaluation since the ——— s still under development.

d) The assay method for ——— CMC pages 135, 172-174, 144-145, is not included in the CMC. The CMC states only that the method is by ——— Also, the — Related Substances method section 1.3 page 172-173, is significantly mistranslated. The sample and reference dilutions are not distinguished. Sample solution "a" should be 20 mg/ml, not —mg/ml. The cited dilutions are not the ones used. The ——— for final reading under normal ——— is not mentioned.

*Raw Material Testing:*

a) References to USP do not reflect actual test methods in many cases. As an example, CMC section 2.12, page 180, for ——— states that all test methods are the same as USP 23, page 848. However, the assay method is an in-house — method, not the USP method, and ——— is not performed although the CMC reports that it this test is conducted.

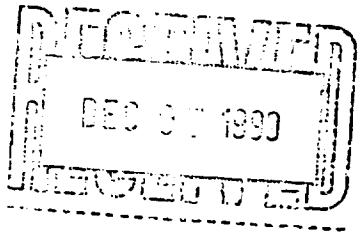
APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE<br>/S/ | EMPLOYEE(S) NAME AND TITLE (Print or Type)<br>Compliance Officer | DATE ISSUED<br>10/28/99 |
|---|---|---|---|

FORM FDA 483 (6/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 2 OF 2 PAGES

[redacted]




Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing & Product Quality, HFD-322
7520 Standish Place, Room 272
Rockville, MD 20855

December 2, 1999

Re: **C.F. No. 9615606**
Manufacturer: Shanghai HuaLian Pharmaceutical Co., Ltd.
Product: Mifepristone
Establishment Investigation: October 25-28, 1999
Inspectional Observations (Form FDA 483): Corrective Action

Dear Sirs:

On behalf of our principals, we are herewith enclosing a response to Inspectional Observations (Form FDA 483) issued at the conclusion of her recent inspection of their plant. Should you require any further information, please do not hesitate to contact the undersigned.

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

Thank you for your attention.

Sincerely,

[redacted]

[redacted]

President

[redacted]

Encl.

cc: [redacted] Compliance Officer, U.S.F.D.A., Philadelphia District
[redacted], V.P., Manufacturing, Danco Investors Group, L.P.
Mr. Li Changfa, Chairman, Shanghai HuaLian Pharmaceutical Co., Ltd.

[redacted]

Shanghai HuaLian Pharmaceutical Co., Ltd. (**C.F. No. 9615606**)
Inspectional Observations - Corrective Action

Inspectional Observations: ———————— to Changfa, Li (October 28, 1999)

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**OBSERVATION:**

"1. Recycled metal drums of the same type and color are used for both virgin solvents and for storing waste solvents. There is no clear policy of marking drums to assure that mix up would not occur. For example, a drum bearing complete labeling for ———————— was filling with waste solvent during this inspection. Other solvents such as ———— and ———————— are received from the central office in drums of the same color that bear minimal identification. Some of these drums are returned to the central office for refilling and others are used for collection of waste with only a minimum of identification."

---

**CORRECTIVE ACTION:**

The procedure followed for the purchase and distribution of dedicated empty drums intended for the storage of organic solvents has been revised in order to establish adequate control of their use.

Also, drums to be used for the disposition of used solvents or process mother liquors, are now painted in a specific color in order to ensure that they will not be confused with drums used for fresh solvents.

For further details please refer to the attached translation of SOP ———— effective November 30, 1999.

**APPEARS THIS WAY ON ORIGINAL**

December 1999

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"2. For [redacted] nd [redacted] analyses performed prior to September 1999, no formal system suitability was performed aside from the initial [redacted] of reference standard."

---

**CORRECTIVE ACTION:**

As noted during the Agency's investigation, system suitability has been routinely performed for [redacted] methods since September 1999.

In the specific case of the final product, data originally obtained for Assay and [redacted] Purity for the ten lots included in the validation of the manufacturing process has been proven to be equivalent to the data generated in November for the corresponding retained samples of the product analyzed following current procedures.

The same equivalence has been established for Residual Solvent data obtained for the same ten lots of Mifepristone.

Please refer to the attached summary of the data obtained for this comparative study.

**APPEARS THIS WAY ON ORIGINAL**

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:** "3. No acceptance criteria have been established for calibration of the [redacted] analyzer although Q.C. approves the monthly calibration runs."

---

**CORRECTIVE ACTION:** Members of the technical support staff for the equipment distributor in Shanghai have been requested to visit the plant and to once again conduct a detailed training session on the operation and calibration procedures to be followed in the use of the [redacted] model.

Subsequently, the attached procedure has been prepared to establish all the required details of the operation and calibration of this equipment and of its acceptance criteria. After the required training of laboratory personnel, this SOP has become effective November 30, 1999.

**APPEARS THIS WAY**
**ON ORIGINAL**

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

*Finished product testing:*

a) The [redacted] method used for release testing of the purified Mifepristone is not described in the CMC."

---

**CORRECTIVE ACTION:**

The CMC Section submitted to the Agency by the Population Council on June 3, 1999 has been reviewed in order to identify any errors and/or omissions in its original version.

Subsequently, an Amendment to this CMC Section has been compiled and submitted to the Agency in order to address these deficiencies[1].

With regard to the specific case transcribed above, please refer to the attached copy of Pages 192-1 & 192-2 including the description of the Mifepristone [redacted] Assay method.

APPEARS THIS WAY
ON ORIGINAL

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[1] For further information, please refer to the attached Revision Summary included with the Amendment submission.

December 1999

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

*Finished product testing:*

b) The specification for residual [redacted] in finished product on CMC page 168 is incorrectly reported as [redacted] The actual specification is

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**CORRECTIVE ACTION:**

As previously indicated, the CMC Section submitted to the Agency by the Population Council on June 3, 1999 has been reviewed in order to identify any errors and/or omissions in its original version and an Amendment to this CMC Section has been compiled and submitted to the Agency in order to address these deficiencies.

With regard to the specific case transcribed above, please refer to the attached copy of revised Page 168 where the [redacted] specifications are now accurately reported.

Please note that the original specifications were incorrectly reported as [redacted] and should have been reported as [redacted] Following the validation of the [redacted] process, the specifications for residual [redacted] have been reduced to [redacted]

APPEARS THIS WAY
ON ORIGINAL

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

*Finished product testing:*

c) The [redacted] analysis for [redacted] on pages 188-189 is incorrect. Flow rates and temperatures are incorrectly reported."

---

**CORRECTIVE ACTION:**

As previously indicated, the CMC Section submitted to the Agency by the Population Council on June 3, 1999 has been reviewed in order to identify any errors and/or omissions in its original version and an Amendment to this CMC Section has been compiled and submitted to the Agency in order to address these deficiencies.

With regard to the specific case transcribed above, please refer to the attached copy of revised Pages 188 & 189 where the [redacted] method of analysis is now accurately described.

**APPEARS THIS WAY ON ORIGINAL**

December 1999

Shanghai HuaLian Pharmaceutical Co., Ltd. **(C.F. No. 9615606)**
Inspectional Observations - Corrective Action

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

*In-process/intermediate test methods:*

a) For [redacted] analyses of the [redacted] intermediate run prior to September 1999, reference standards were only run once per 5 samples. The data from this standard run was used in calculations for all subsequent samples run on different days."

---

**CORRECTIVE ACTION:**

The procedures followed since September 1999 require alternate [redacted] of working standards and test solutions of any analyte following the performance of the pertaining method's system suitability.

APPEARS THIS WAY
ON ORIGINAL

December 1999

Inspectional Observations: [redacted] to Changfa, Li (October 28, 1999)

---

**OBSERVATION:**

"4. There are numerous errors and/or omissions in the CMC methods filed for NDA 20-687 for Mifepristone including, but not limited to, the following:

*In-process/intermediate test methods:*

b) There is limited resolution of the [redacted] major impurities from the main reactant in the [redacted] method for in-processing monitoring of the [redacted] reaction in synthesis of the key intermediate, [redacted]

---

**CORRECTIVE ACTION:**

An improved method has been developed to monitor the completion of the conversion of the starting material [redacted] into the process's [redacted] This new method has been described in the attached Pages 142 and 142-1 of the CMC Section Amendment recently submitted to the Agency.

Please refer to the attached method's validation protocol and report. Also attached, please find comparative [redacted] obtained with both methods for lot 991103 and for a mixture of working standards documenting the improved resolution between the [redacted]

APPEARS THIS WAY
ON ORIGINAL

December 1999

SEP 1 1 1996

NDA 20-687
Mifepristone

The Population Council
August 28, 1996

Medical Officer's Summary of Safety Update Dated
June 20, 1996

Included in the Safety Update Report received June 27, 1996 are two new clinical study reports as well as new information regarding study reports previously submitted.

The first new clinical study report is entitled, "The Efficacy and Safety of Mifepristone 600 mg in a Single Dose in Combination with Intravenously Administered Sulprostone (Nalador) in Therapeutic Termination of Second Trimester Pregnancy". The second new clinical report is entitled "Role of Cortisol in the Thermal Response to Alimentation: Effect of Mifepristone" and consisted of twelve healthy, male volunteers, six of whom received a single 600 mg tablet and six of whom received a placebo.

Neither of the two new clinical study reports reveal any additional safety concerns not identified in the two pivotal clinical studies.

Newly completed clinical trials include three studies of labor induction, two studies of breast cancer, and the United States clinical trials of early pregnancy termination. Laboratory data from these completed studies have not yet been analyzed and, therefore, no information on laboratory data are reported in this safety update. Final data analysis and study reports for these six studies have not been completed. The results for termination of pregnancy studies conducted in the United States are expected to be in full agreement with the two pivotal clinical studies. No unanticipated safety issues were raised in these studies. Preliminary examination of information from the United States studies as it was forwarded weekly from the clinics directly to the sponsor during the course of the trials indicates that the final, analyzed results will be similar to those obtained in similar clinical trials of the same medical regimen.

The literature update includes eleven articles published in 1995 and one article published in 1996. Three articles are of particular interest. One is the publication of one of the pivotal clinical studies (FF/92/486/24) by Aubeny et.al. The second is entitled "A Comparative Analysis of Fall in Hemoglobin Following Abortions Conducted By Mifepristone (600 mg) and Vacuum Aspiration" by Thonneau et. Al. The investigators found significant blood loss in the two weeks following abortions by the mifepristone/sulprostone protocol while hemoglobin concentrations remained stable in women who had vacuum aspiration. Women who took mifepristone experienced a mean fall of 0.7 g/dl in hemoglobin two weeks after the abortion. The third article entitled "Clinical, Hormonal, and Sonographic Predictors of Successful RU-486-Induced Abortions" was by Menashe et.al. A small hematoma, seen as a localized detachment of the gestational sac, was observed in the decidua capsularis in women who aborted successfully. A significant decrease in plasma levels of estradiol and progesterone and significantly increased cortisol levels in the plasma of the patients who aborted were observed by the seventh day following treatment.

Table four of the Safety Update Report contains adverse reactions from all sources reported to Roussel Uclaf which were summarized in the quarterly line listings covering July 1, 1995 to September 30, 1995; October 1, 1995 to December 31, 1995; January 1, 1996 to March 31, 1996 and reported in the Periodic Safety Update No. 3 dated January 1996 for the period June 1, 1995 to November 30, 1995.

Of a total of forty eight patient reports of adverse experiences listed in Table 4, twenty-eight were reported from patients enrolled in the United States studies (protocols 166A and B). Of these twenty-eight reports, nineteen were metrorrhagia, three were abdominal pain, two were dehydration, and there were one each of depression, viral meningitis, vomiting, and syncope. Vacuum aspiration or D&C was performed in twelve cases of metrorrhagia and a blood transfusion was given in one case of metrorrhagia. Concomitant hypotension was also reported in four patients with severe metrorrhagia. The patient with syncope presented with a marked vasovagal reaction fifteen minutes after misoprostol administration.

In the section of the Safety Update Report entitled "Tolerance of RU 486 During United States Studies" there is Table 1 which was submitted to the sponsor by Russell Uclaf June 7,1995 which indicates that there were forty-seven serious adverse events plus 8 non serious adverse events in the United States studies (protocols 166 A and B). Table 2 indicates that of the forty-seven serious adverse events forty-one were related to bleeding, two to hypotension, and one each to vomiting, chest pain, infection, and accidental injury.

→ PAR 8/29/96 Review

Two deaths have occurred in clinical trials conducted by Roussel Uclaf. One was a male in a study evaluating mifepristone in the treatment of Cushing syndromes by ectopic ACTH secretion or adrenal tumor. The other was an eighty-three year old female with an unresectable meningioma who suffered a stoke like event leading to death. Seven other deaths were reported in patients enrolled in compassionate use protocols. One of these deaths was a seventy-one year old woman with an acute myocardial infarction.

Also included is a half page document entitled "Notifications Report to Roussel Uclaf from Study English PMS" which lists seven reactions occurring in five patients. There were three reports of uterine hemorrhage, one incomplete abortion with bleeding, one convulsion, one congenital nail disorder, and one report of lack of efficacy.

Also included is a section entitled "New Foreign Marketing Information" which consists only of a core product information document from the product manufacturer revised in March 1995.

Since the start of the use of mifepristone until November 30, 1995, Roussel Uclaf has recorded fifty-three cases of continued pregnancy after the intake of mifepristone for early pregnancy termination (alone or associated with a postaglandin analog).

Among these fifty-three cases:

Nineteen pregnancies were delivered at term (or close to it):

Fifteen were uneventful pregnancies with children normal at birth.
One was normal but born prematurely (33-34 weeks) from caesarean section
One was normal except for common slight bilateral talipes.
One case involves unilateral fingernail defects.
One child was reported as strictly normal at birth but it was known that when she was three months old, the infant was diagnosed as having an autoimmune disorder with chronic giant cell hepatitis and immunohemolytic anemia and later died of severe infectious pneumonia likely exacerbated by immuno-suppressive drugs. The reporting physician's opinion (an expert in teratogenicity) was that the onset of the autoimmune disorder was coincidental and that the role of mifepristone could be reasonably excluded.

In fifteen cases information on further condition of the fetus was made available, mainly in the cases where pregnancy is known to have been terminated later:

In nine cases, termination was performed voluntarily and information either from histologic examination or from ultrasound was that the fetus was normal.

In one case, at therapeutic termination the fetus was noted to have sirenomelia associated with other fetal malformations. The opinion of the consulting embryologists to whom the case was submitted by Roussel Uclaf was that the role of mifepristone was very unlikely. This case has been published (Pons J.C. and all : Lancet, 1991, 328: 763).

In five cases of ongoing pregnancy, the latest available information during second trimester examination indicated normal pregnancy and fetus development.

In six cases, no information on the fetus could be obtained but pregnancy was known to have been terminated later.

In thirteen cases, no further information was made available; in most cases patients were lost to follow-up, and in some cases pregnancy is still ongoing.

**Comment**: This Safety Update does not reveal any unexpected, unanticipated safety issues that were not made known in the original submission of the NDA.

/S/

Concur: /S/ MD 9/11/96

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Population Council

2. DATE OF SUBMISSION
July 16, 1997

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 327-8748

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Mifepristone Tablets

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Induction of abortion

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
189

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

| PROTOCOL AMENDMENT(S): | INFORMATION AMENDMENT(S): | IND SAFETY REPORT(S): |
|---|---|---|
| ☐ NEW PROTOCOL | ☐ CHEMISTRY/MICROBIOLOGY | ☐ INITIAL WRITTEN REPORT |
| ☐ CHANGE IN PROTOCOL | ☐ PHARMACOLOGY/TOXICOLOGY | ☐ FOLLOW-UP TO A WRITTEN REPORT |
| ☐ NEW INVESTIGATOR | ☐ CLINICAL | |

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ TREATMENT IND 21 CFR 312.85(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | REC'D JUL 17 1997 HFD-150 EVALUATION AND RESEARCH | DIVISION ASSIGNMENT: |

FORM FDA 1571 (1/97) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

MIF 005415

## CONTENTS OF APPLICATION

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

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
- ☐ ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED. Please refer to Submissions 100 and 163

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Ann Robbins, Ph.D.
Scientist
Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Ann Robbins, Ph.D.
Scientist
Population Council

Irving M. Spitz, M.D.
Senior Scientist
Population Council

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Ann Robbins, Ph.D.

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Ann Robbins

18. ADDRESS *(Number, Street, City, State and Zip Code)*

Population Council
1230 York Avenue
New York, NY 10021

19. TELEPHONE NUMBER *(Include Area Code)*

(212) 327-8748

20. DATE

07/16/97

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)



Please DO NOT RETURN this application to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21; CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* December 31, 1999
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

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Population Council

2. DATE OF SUBMISSION
July 16, 1997

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8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

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SERIAL NUMBER
189

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☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
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☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

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☒ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | REC'D JUL 17 1997 HFD-150 EVALUATION AND RESEARCH | DIVISION ASSIGNMENT: |

FORM FDA 1571 (1/97) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

MIF 005417

12. **CONTENTS OF APPLICATION**

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- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
- ☐ ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED. Please refer to Submissions 100 and 163

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Ann Robbins, Ph.D.
Scientist
Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Ann Robbins, Ph.D.
Scientist
Population Council

Irving M. Spitz, M.D.
Senior Scientist
Population Council

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Ann Robbins, Ph.D.

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Ann Robbins

18. ADDRESS *(Number, Street, City, State and Zip Code)*

Population Council
1230 York Avenue
New York, NY 10021

19. TELEPHONE NUMBER *(Include Area Code)*

(212) 327-8748

20. DATE

07/16/97

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date:* February 29, 1996.
*See OMB Statement on Reverse.*

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
The Population Council

2. DATE OF SUBMISSION
August 23, 1996

3. ADDRESS *(Number, Street, City, State and Zip Code)*
1230 York Avenue
New York, NY 10021

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 327-8748

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Mifepristone Tablets

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
Induction of abortion

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
167

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND (21 CFR 312.35) ☐ TREATMENT PROTOCOL (21 CFR 312.35) ☐ 30-DAY REQUEST/NOTIFICATION (21 CFR 312.23)

FOR FDA USE ONLY

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | IND NUMBER ASSIGNED: |
|---|---|---|
| | CENTER FOR DRUG REC'D AUG 26 1996 HFD-150 EVALUATION AND RESEARCH | DIVISION ASSIGNMENT: |

FORM FDA 1571 (1/96) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

MIF 005419

# Electronic Mail Message

**Date:** 5/12/97 3:04:16 PM
**From:** [redacted]
**To:** [redacted]
**Subject:** RU 486

[redacted]

RU 486 hasn't been approved yet has it? I got a call from FDA's NY-DO saying they heard it was approved and it was available in a NY clinic. Please advise, so I can relay the correct information to the field.

Thanks!!
[redacted], HFD-150)

DCT ADVERSE REACTION FORM FOR INVESTIGATIONAL AGENTS

ADR # _____ (Assigned by NCI)

Person completing this form _____ Date _____

Physician responsible for this report _____

I.

A. **Demographics**

Pt ID # _____ Age _____ Sex _____ Date of initial Dx _____

Malignancy _____
Site of primary _____ PS (at start of study) ___
Site(s) of metastatic disease _____
Concurrent Non-Malignant Disease and Non-Protocol Medications? yes ___ no ___

B. **Drug Information**

Drug name _____
Source of drug: NCI _____ Other _____ Specify _____
Type of reaction _____ Toxicity grade _____
Date of reaction _____ Date IRB notified _____
NCI Protocol # _____ Attending physician (Investigator) _____
Phase of study _____ Institution _____ Phone _____

Protocol Treatment (include all agents)

| Drug | Dose | Schedule | Route |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

Date of first course _____ Number of courses _____
Date last course started _____ Date of therapy associated with ADR _____

| Prior therapy (drug, radiation, relevant surgery) | Dates of prior therapy |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |

II. **Documentation of Reaction**

A. Non-Myelosuppressive Toxicity and Previously Unknown Myelosuppression

1. Description of reaction and temporal relationship to Investigational Drug administration.

2. Physical findings and laboratory data documenting toxicity (e.g. bilirubin, creatinine, including baseline, worst, and recovery values).

3. Complication and sequelae (If death, was an autopsy obtained?)

4. Past history of organ dysfunction

5. Rechallenge with agent? yes ___ no ___

If 'yes', describe outcome. _____

B. Myelosuppression (Previously known or unknown)

1. Laboratory data documenting myelosuppression.

| | Baseline Date - Value | Nadir Date - Value | Recovery Date - Value |
|---|---|---|---|
| WBC or PMN | _____ _____ | _____ _____ | _____ _____ |
| Platelets | _____ _____ | _____ _____ | _____ _____ |
| Hgb or Hct | _____ _____ | _____ _____ | _____ _____ |

2. Complications, treatment and sequelae (e.g. infection, hemorrhage).

C. Grade of Toxicity and Reporting Requirements (check one)

1. Previously unknown toxicities

a. fatal _____ b. life-threatening _____ **Report by telephone within 24 hrs (301) 496-7957**

b. Grade I ___ Grade II ___ Grade III ___ **Send DCT Adverse Reactions Form within 10 days**

2. Previously known non-myelosuppressive toxicities

a. fatal _____ b. life-threatening _____ **Send DCT Adverse Reactions Form within 10 days**

3. Previously known myelosuppressive toxicities

a. fatal _____ **Send DCT Adverse Reactions Form within 10 days**

D. Investigator's Assessment (Assess each investigational if more than one is used)

| | IND | NON-IND | DISEASE | Action Taken | Therapy Required |
|---|---|---|---|---|---|
| Unrelated | ____ | ____ | _____ | None ____ | None ____ |
| Not likely related | ____ | ____ | _____ | Dose Reduced ____ | Symptomatic ____ |
| Possibly related | ____ | ____ | _____ | Dose Withheld ____ | Supportive ____ |
| Probable related | ____ | ____ | _____ | Drug Discontinued ____ | Intensive ____ |
| Definitely related | ____ | ____ | _____ | | |

E. I hereby certify that the information contained in this report is correct and complete to the best of my knowledge.

Signature of responsible physician _____ Date _____

SHMC 6-91

# CDER EXECUTIVE SECRETARIAT STAFF

## METROPARK NORTH, BUILDING I

**DATE:** 3-29-93

**TO:** _____ **PHONE#** _____

**FROM:** _____ **HFD#**

**NUMBER OF PAGES** 2 + COVER

**COMMENTS:** You Are Right!! It's not yet rescinded. - /S/

# Presidential Documents

Memorandum of January 22, 1993

## Importation of RU-486

Memorandum for the Secretary of Health and Human Services

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristone—commonly known as RU-486—from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (*See* FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectivaly bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the Federal Register.

William J. Clinton

THE WHITE HOUSE,
*Washington, January 22, 1993.*

[FR Doc. 93-2975
Filed 2-3-93; 1:20 pm]
Billing code 3195-01-M

Editorial note: The Secretary of Health and Human Services is publishing a document relating to this memorandum in Part V of this issue. For the President's remarks on signing this memorandum, see p. 65 of the *Weekly Compilation of Presidential Documents.*

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Office of the Secretary

### Actions Regarding Family Planning Service Projects, Transplantation of Human Fetal Tissue, and Importation of the Drug Mifepristone

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: In accordance with directives of President Clinton dated January 22, 1993, I have today ordered that the following actions be taken:

(1) The Standard of Compliance for Abortion-Related Services in Family Planning Service Projects (the "Gag Rule") is to be suspended, pending the publication of regulations to formally rescind the rule.

(2) The temporary moratorium imposed March 22, 1988, by the Assistant Secretary for Health and continued by the previous Secretary on November 2, 1988, prohibiting Federal funding of research involving transplantation of human fetal tissue from induced abortions, is to be rescinded.

(3) Food and Drug Administration Import Alert 66-47, importation of the drug Mifepristone ("RU-486") is to be immediately and thoroughly reviewed regarding the health and safety implications of potential import of the drug for personal use.

FOR FURTHER INFORMATION CONTACT: Audrey Manley, M.D., M.P.H., Acting Assistant Secretary for Health, Public Health, Public Health Service (202) 690-7694.

SUPPLEMENTARY INFORMATION: *The Standard of Compliance for Abortion-Related Services in Family Planning Service Projects (the "Gag Rule")*—In documents printed elsewhere in this issue of the Federal Register, the amendments to 42 CFR part 59, subpart A, published on February 2, 1988 (53 FR 2922)—commonly referred to as the "Gag Rule"—are suspended and new regulations are proposed to govern the Family Planning program established under Title X of the Public Health Service Act.

*Federal Funding of Fetal Tissue Transplantation Research*—This notice advises the public that the PHS is directed to rescind the moratorium imposed on March 22, 1988 which prohibits Federal funding of research involving transplantation of human fetal tissue from induced abortions. Such funding may be provided, subject to the procedures and protections which govern Federal support of biomedical research, and subject to guidelines as recommended by a National Institutes Health advisory committee. Interim guidelines are to be prepared immediately by the Director of the National Institutes of Health, as recommended by the committee, to assure that Federal support of such research does not encourage the choice of induced abortion.

*FDA Alert 66-47 Excluding Importation of the Drug Mifepristone ("RU-486")*—The FDA has been directed to initiate immediate and thorough review, directed at the health and safety implications of potential import of the drug for personal use. Findings of the review are to be reported promptly to the Secretary. If sufficient evidence does not exist to warrant exclusion of the RU-486 from the list of drugs that qualify for the personal use importation exemption, this import alert shall be rescinded. At the same time, FDA is directed to promptly assess initiatives to promote testing of RU-486 or other antiprogestins in the United States, and, as appropriate, licensing and manufacturing in this country, and report on options to the Assistant Secretary for Health and the Secretary.

The President's memoranda are published in Part IV of this Federal Register issue.

Dated: February 2, 1993.

Donna E. Shalala,

Secretary.

[FR Doc. 93-2736 Filed 2-3-93; 1:18 pm]

BILLING CODE 4160-01-M

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

FEB 5 1993

TO: Commissioner of Food and Drugs

FROM: Acting Assistant Secretary for Health

SUBJECT: Importation of RU-486

In accordance with the attached memoranda from the President and the Secretary, please analyse existing evidence to determine if the exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption is warranted. If sufficient evidence does not exist, please take immediate steps to rescind the RU-486 import alert.

In addition, you are requested to assess initiatives by which testing, licensing, and manufacturing of RU-486 and other antiprogestins can be promoted in the United States.

The Secretary has requested that I direct you to proceed with all possible speed in these matters, and has asked that I report back to her regarding the import alert, and options to promote the testing of RU-486 or other antiprogestins. Accordingly, please report to me as soon as possible with respect to these matters.

Attachments

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

FEB 1 1993

BEST POSSIBLE COPY

TO: The Acting Assistant Secretary for Health

FROM: The Secretary

SUBJECT: Importation of RU-486

In accordance with the attached memorandum from the President, you should instruct the Food and Drug Administration to initiate an immediate and thorough review of the potential import of the drug Mifeprastine (RU-486) for personal use. The purpose of this analysis is to determine if sufficient evidence exists to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. The review should focus on health and safety implications of the drug and findings should be reported to the Secretary promptly. If sufficient evidence does not exist to warrant exclusion of the RU-486 from the list of drugs for personal use importation exemption, this import alert shall be rescinded.

At the same time, FDA is directed to promptly assess initiatives to promote testing of RU-486 or other antiprogestins in the United States, and as appropriate, licensing and manufacturing in this country, and report on options to the Assistant Secretary for Health and the Secretary.

Donna E. Shalala

Attachment

APPEARS THIS WAY
ON ORIGINAL

MIF 005454

THE WHITE HOUSE

WASHINGTON

January 22, 1993

BEST POSSIBLE COPY

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristine -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (See FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 effectively bans the importation into this Nation of a drug that is used in other nations as a nonsurgical means of abortion.

I am informed that in excluding RU-486 from the personal use importation exemption, the FDA appears to have based its decision on factors other than an assessment of the possible health and safety risks of the drug. Accordingly, I hereby direct that you promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. Furthermore, if the FDA concludes that RU-486 meets the criteria for the personal use importation exemption, I direct that you immediately take steps to rescind Import Alert 66-47.

In addition, I direct that you promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 or other antiprogestins.

You are hereby authorized and directed to publish this memorandum in the Federal Register.

William J. Clinton

# CLINICAL TRIAL
# SERIOUS ADVERSE EVENT FORM

➤ TO BE COMPLETED IN CASE OF :

- Life-threatening event
- Death
- Cancer/congenital anomaly
- Event leading to hospitalisation or prolongation of hospitalisation
- Event resulting in chronic condition/sequelae
- Overdose

<u>WHATEVER RELATIONSHIP TO STUDY DRUG</u>

➤ The first copy must be sent to the monitor, the second must be kept by the investigator, the third must be enclosed in the case record form.

➤ Please be as complete and as precise as possible when describing the course of the patient's condition.
If possible, please join a copy of the relevant investigations and forward a hospitalisation report when available.

# CLINICAL TRIAL
# SERIOUS ADVERSE EVENT FORM

**STUDY/INVESTIGATOR**

Protocol number : ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Center number : ⌊_⌊_⌊_⌊_⌋

Indication : _____

_____

Investigator's name : _____

Address : _____ Country : _____

_____

_____

**PATIENT**

Number allocated in the study ⌊_⌊_⌊_⌊_⌊_⌋

Local drug surveillance number ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

| Initials | Age | Sex | Weight | Height |
|---|---|---|---|---|
| ⌊_⌊_⌊_⌋ | ⌊_⌊_⌋ y ⌊_⌊_⌋ m | M ⌊_⌋ F ⌊_⌋ | ⌊_⌊_⌋ kg ⌊_⌊_⌊_⌋ g | ⌊_⌊_⌋ m ⌊_⌊_⌋ cm |

Occupation : _____ Ethnic origin : _____

Previous relevant history : _____

_____

_____

_____

Previous Intolerance to drugs : No ⌊_⌋ Yes ⌊_⌋ which drugs ? _____

_____

Unknown ⌊_⌋

**ADVERSE EVENT**

Date of onset ⌊_⌊_⌋ D ⌊_⌊_⌋ M ⌊_⌊_⌋ Y

Description : _____

_____

Hospitalisation (or prolongation of hospitalisation) necessary ? ⌊_⌋ yes ⌊_⌋ no

Treatment : _____

_____

_____

OUTCOME : Complete recovery ⌊_⌋ Chronic condition or sequelae ⌊_⌋

Not yet resolved ⌊_⌋ Unknown ⌊_⌋

Death ⌊_⌋

➤ Date ⌊_⌊_⌋ D ⌊_⌊_⌋ M ⌊_⌊_⌋ Y

➤ Autopsy ⌊_⌋ yes ⌊_⌋ no

**CASE SUMMARY**

(Precise description of history with respect to the adverse event)

## STUDY DRUG

Name _____

or Code ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Route _____

Daily dose regimen : dose ⌊_⌊_⌋ unit ⌊_⌊_⌊_⌋ frequency _____

Therapy date : from ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y to ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y Ongoing ⌊_⌋

**Action taken with study drug after the event :**

Continued same dose ⌊_⌋ Stopped ⌊_⌋ Decreased ⌊_⌋ NA* ⌊_⌋

**Immediate results :**

Improvement ⌊_⌋ No change ⌊_⌋ Aggravation ⌊_⌋ Uninterpretable ⌊_⌋ NA* ⌊_⌋

**Rechallenge**

No ⌊_⌋ Yes ⌊_⌋ NA* ⌊_⌋

Date : ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y

**Recurrence of event :**

No ⌊_⌋ Yes ⌊_⌋ NA* ⌊_⌋

Uninterpretable ⌊_⌋

* Not applicable

## CONCOMITANT DRUGS

| Drug | Daily dose | From | To | Indication |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

## CAUSAL RELATIONSHIP

**Doctor's assessment :**

Unrelated ⌊_⌋ Unlikely ⌊_⌋

possible ⌊_⌋ probable ⌊_⌋ highly probable ⌊_⌋

not assessable ⌊_⌋ explain why _____

This form was filled out ➤ on ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y

➤ by (print)

➤ position

➤ Monitor's name and signature : _____

IND [redacted]
RU486

The Population Council
October 2, 1989

Medical Officer's Review of Submission Dated September 22, 1989

Submission dated September 22, 1989 is a follow-up report pursuant to our letter of August 15, 1989 to the sponsor requesting followup reports of the five patients in the Los Angeles clinic where SGPT elevations at day 14 or 15 were still apparent.

| Subject | Dosage | Day | SGPT |
|---|---|---|---|
| 06043 | 100 mg/d x 7 | 15 | 63.0 |
| | | 22 | 19.0 |
| 06095 | 50 mg/d x 7 | 08 | 88.0 |
| | | 15 | 97.0 |
| | | 22 | 36.0 |
| 06103 | 100 mg/d x 4 | 14 | 48.0 |
| | | 19 | 19.0 |

There was no follow-up on patients 06111 and 06100. Patient 06111 who received 100 mg/d x 4 had an SGPT of 73 on day 8 which had dropped only to 69 on day 15 and patient 06100 who received a single 600 mg dose had an SGPT of 71 on day 14. From the information on the three patients followed, it appears that SGPT returns to normal by day 22.

/S/

HFD-510/ [redacted]

/S/ 10-10-89

APPEARS THIS WAY
ON ORIGINAL

A.F. _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Honorable Barbara F. Vucanovich
House of Representatives
Washington, D.C. 20515

JUL 31 1989

Dear Ms. Vucanovich:

This is in response to your letter of July 7, 1989, on behalf of _____ concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

An investigational new drug (IND) application acceptable to the FDA is required of a sponsor (e.g., a drug manufacturer or a clinical investigator) to study the safety and effectiveness of an unapproved new drug. When the sponsor determines that adequate and well-controlled studies have been performed, which reflect favorably on a new drug's safety and effectiveness, the sponsor then submits that information, together with adequate information on manufacturing procedures and controls, in a new drug application to FDA. After a comprehensive review by the FDA, the NDA is either approved or not approved; upon approval the drug may be marketed.

We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

2 Enclosures
"Clinical Testing . . ."
"A Primer on New . . ."

cc: HFW-10(2)
R/D: _____ :6/29/89:F/D: _____ :7/26/89
F/T:vaj:7/31/89:( _____ :RU486)

FILE COPY

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
|---|---|---|---|---|---|---|---|---|
| HFW-12 | 1st | 8/2 | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

MIF 005462

BARBARA F. VUCANOVICH
2ND DISTRICT, NEVADA

COMMITTEE ON INTERIOR AND INSULAR AFFAIRS
COMMITTEE ON HOUSE ADMINISTRATION
SELECT COMMITTEE ON CHILDREN, YOUTH AND FAMILIES
CONGRESSIONAL TRAVEL AND TOURISM CAUCUS
ENVIRONMENTAL AND ENERGY STUDY CONFERENCE

# CONGRESS OF THE UNITED STATES
## HOUSE OF REPRESENTATIVES
## WASHINGTON, D.C. 20515

206 CANNON BUILDING
WASHINGTON, D.C. 20515
(202) 225-6155

FEDERAL BUILDING
300 BOOTH STREET, SUITE 3038
RENO, NEVADA 89509
(702) 784-5003

401 RAILROAD ST. #307
ELKO, NEVADA 89801
(702) 738-4064

2200 CIVIC CENTER DRIVE
POST OFFICE BOX A
NORTH LAS VEGAS, NV 89030-1320
(702) 399-3555

July 7, 1989

Mr. Frank E. Young
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Young:

I am writing you to request your assistance in a matter that has recently been brought to my attention.

One of my constituents, _____ has written me regarding the drug RU-486. I would greatly appreciate your reviewing and addressing the concerns of _____ I have enclosed a copy of the letter for your convenience.

Thank you in advance for your time and attention to this matter.

Sincerely,

Barbara

BARBARA F. VUCANOVICH
Member of Congress

BFV:ml
Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

R.F. _____ FI

JUL 06 1989

The Honorable Dante B. Fascell
House of Representatives
Washington, D.C. 20515

Dear Mr. Fascell:

This is in response to your letter of June 7, 1989, on behalf of _____ concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

An investigational new drug (IND) application acceptable to the FDA is required of a sponsor (e.g., a drug manufacturer or a clinical investigator) to study the safety and effectiveness of an unapproved new drug. When the sponsor determines that adequate and well-controlled studies have been performed, which reflect favorably on a new drug's safety and effectiveness, the sponsor then submits that information, together with adequate information on manufacturing procedures and controls, in a new drug application to FDA. After a comprehensive review by the FDA, the NDA is either approved or not approved; upon approval the drug may be marketed.

We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

2 Enclosures
"Clinical Testing . . ."
"A Primer on New . . ."

cc: HFW-10(2)
R/D: _____ :6/29/89 _____ -RU486)
F/T:crw:6/29/89

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
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| HFW2 | /S/ | 6/30 | | | | | | |
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FILE COPY

MIF 005464

*U.S. GPO: 1989-619-669

DANTE B. FASCELL
19TH DISTRICT, FLORIDA

FOREIGN AFFAIRS COMMITTEE
CHAIRMAN

ARMS CONTROL, INTERNATIONAL
SECURITY AND SCIENCE SUBCOMMITTEE
CHAIRMAN

SELECT COMMITTEE ON NARCOTICS
ABUSE AND CONTROL
MEMBER

CHARLES R. O'REGAN
ADMINISTRATIVE ASSISTANT

COMMISSION ON SECURITY AND
COOPERATION IN EUROPE
MEMBER

NORTH ATLANTIC ASSEMBLY
CHAIRMAN
HOUSE DELEGATION

CANADA—UNITED STATES
INTERPARLIAMENTARY GROUP
MEMBER, U.S. DELEGATION

# Congress of the United States

## House of Representatives

## Washington, DC 20515

June 7, 1989

Mr. Hugh C. Cannon, Associate Commissioner
for Legislative Affairs
Food and Drug Administration
5600 Fisher's Lane, Room 1555
Rockville, Maryland 20857

Dear Mr. Cannon:

Enclosed is a copy of correspondence from one of my constituents.

It would be greatly appreciated if you would accord the comments in the letter every consideration and provide me with a report on the matter.

Many thanks for your assistance.

Sincerely,

Dante B. Fascell

DANTE B. FASCELL
Member of Congress

DBF/BT

Enclosure

APPEARS THIS WAY
ON ORIGINAL

MIF 005465

DEPARTMENT OF HEALTH AND HUMAN SERVICES

A.F. _____ FIL

The Honorable Doug Bereuter
House of Representatives
Washington, D.C. 20515

JUL 06 1989

Dear Mr. Bereuter:

This is in response to your letter of June 10, 1989, on behalf of _____ concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

3 Enclosures
Constituent's ltr
"Clinical Testing . . ."
"A Primer on New . . ."

cc: HFW-10(2)
R/D: _____:6/29/89
F/T:crw:6/29/89 _____ -RU486)

FILE COPY

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| HFW | [illegible] | 6/30 | | | | | | |

MIF 005466

151065
170536

The Honorable
U. S. House of Representatives
Washington D. C.20515

Dear Representative,

I am writing to you to oppose any attempts to restrict the Food and Drug Administration from further testing of the drug RU-486. This drug provides an alternative to surgical abortion. Although first trimester abortion is currently one of the safest surgical procedures in the United States, RU-486 decreases or eliminates many of the occasional complications which can occur with any kind of surgery.

American women ought to have access to the best possible health care, and this includes making sure the safest methods are available for all legal medical procedures. Please don't allow a vocal minority to deprive all women of advances in medical technology.

Sincerely yours,

151

Name

Addr

**HOUSE OF REPRESENTATIVES, U.S.**
WASHINGTON, D.C.

June 10, 1985

Cong. Liaison
FDA
HHS
200 Ind. Ave. S.W.
Wash. D.C. 20201

The attached communication is submitted for your consideration, and to ask that the request made therein be complied with, if possible.

If you will advise me of your action in this matter and have the letter returned to me with your reply, I will appreciate it.

APPEARS THIS WAY ON ORIGINAL

Very truly yours,

Doug Bereuter
M.C.

Nebr. / First
District.

attn: Wrexie Logan

# United States Senate

COMMITTEE ON APPROPRIATIONS
WASHINGTON, DC 20510-6025

June 19, 1989

Mr. Hugh C. Cannon
Associate Commissioner for
Legislative Affairs
Food and Drug Administration
1555 Parklawn Building
5600 Fishers Lane
Bethesda, Maryland 20857

Dear Mr. Cannon:

I have been contacted by constituents concerned, and interested in obtaining more information, about RU-486, the abortifacient drug developed by the French pharmaceutical firm Roussel Uclaf.

It would be appreciated if you would look into this matter and provide me with your comments which may serve as the basis for a reply to my constituents.

Thank you in advance for your attention to this matter.

Sincerely yours,

Robert C. Byrd

RCB:dw
Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

A.F. _____ FILE

The Honorable Robert C. Byrd
United States Senate
Washington, D.C. 20510

[redacted] 6 1989

Dear Senator Byrd:

This is in response to your letter of June 19, 1989, on behalf of your constituents who are interested in the unapproved new drug, ~~RU-486~~.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure your constituents that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

2 Enclosures
"Clinical Testing . . ."
"A Primer on New . . ."

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

cc: HFW-10(2) 6/29/89 RU486)
crw:6/29/89

FILE
COPY

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*U.S. GPO: 1989-619-669

MIF 005470

A. F. ___ FILE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUN 15 1989

The Honorable Lee H. Hamilton
House of Representatives
Washington, D.C. 20515

Dear Mr. Hamilton:

This is response to your inquiry of May 15, 1989, on behalf of _____, concerning the unapproved drug, RU-486

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

It is also important to point out that FDA does not actually do the clinical testing of drugs before they are marketed. Pharmaceutical manufacturers, the National Institutes of Health, and other research institutions across the country carry out programs to identify, develop and test drugs. It is FDA's responsibility to review and analyze the results of the testing to determine if a drug is safe and effective for widespread marketing for use by the general public.

6414

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
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| HFA-12 | FST | 6/15 | | | | | | |
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FILE COPY

MIF 005471

*U.S. GPO: 1989-619-666

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

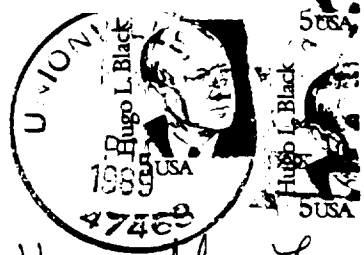
Enclosure
Constituent's Ltr

cc: HFW-10(2)
HFW-12 w
F/d: :6/1/89
R/t:var:6/7/89( RU486)
F/T:var:6/9/89

APPEARS THIS WAY
ON ORIGINAL

Thymus vulgaris
~~food~~ instead of sauce
for the use in health.
30 Apr. '89 Dioscorides, 1st c. A.D.

I urge you to oppose any and all attempts to prevent the FDA from testing RU-486. We must not let a small minority prohibit access to this drug, ~~we~~ which could be enormously beneficial to U.S. women. . .




The Honorable Lee Hamilton
U.S. House of Representatives
Washington
DC 20515

The Honorable Lee H. Hamilton
House of Representatives
Washington, D.C. 20515

Dear Mr. Hamilton:

This is response to your inquiry of May 15, 1989, on behalf of _____ concerning the unapproved drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

It is also important to point out that FDA does not actually do the clinical testing of drugs before they are marketed. Pharmaceutical manufacturers, the National Institutes of Health, and other research institutions across the country carry out programs to identify, develop and test drugs. It is FDA's responsibility to review and analyze the results of the testing to determine if a drug is safe and effective for widespread marketing for use by the general public.

we hope these comments are helpful. If we can be of furtner service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosure
Constituent's Ltr

cc: HFW-10(2)
HFW-12

F/T:var:6/9/89

MAY 22 1989

NOTE TO: Office of Legislative Affairs

SUBJECT: Congressional Correspondence

The attached correspondence arrived in the Office of Management and Operations on May 18, 1989 through messenger envelopes. We believe these documents should be directed to your office for action.

/S/

Attachment

APPEARS THIS WAY
ON ORIGINAL

A.F. FILE

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

The Honorable Robert K. Dornan
House of Representatives
Washington, D.C. 20515

JUN 09 1989

Dear Mr. Dornan:

I write to respond to your letter of May 5, 1989, also signed by several of your colleagues, relating to the Food and Drug Administration's (FDA) policy on the importation of unapproved drugs into the United States. Specifically, you asked whether this policy would allow the mail order of RU-486 (mifeprisone), and other abortifacient drugs which are not approved for marketing in the United States.

For many years FDA has, as a matter of discretion, permitted individuals to bring into the United States, for their personal use, quantities of drugs sold abroad but not approved in the United States. Over the years numerous patients, family members and physicians have urged the Agency to permit this personal importation of various drugs out of compassion for the individual patients involved, many of whom have serious or life threatening disease. I should note that numerous Members of Congress have also urged FDA to allow the personal importation of drugs out of compassion for their constituents.

Personal use quantities are generally considered to be amounts for a patient's treatment for three months or less. Imports involving larger quantities are generally not permitted as they could lead to commercialization.

As you know, in July 1988, the Agency issued written guidance to our field offices to clarify the policy's applicability to mail imports, and to ensure that our policies and practices in this important area are consistent throughout the country. The guidance states that unapproved drugs may be imported if there is no unreasonable safety risk or evidence of fraud, and other criteria are met relating to personal use, quantity, and other factors.

5414

FILE COPY

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*U.S. GPO: 1988-216-488

MIF 005477

We do not believe that this policy can be appropriately applied to the importation of RU-486 because use of the product could present an unreasonable safety risk, and we have recently issued an import alert to this effect. The intended use of this drug makes it likely it would be used without benefit of supervision of a physician, and indiscriminate or unsupervised use could be hazardous to the patient's health because the drug has potential side effects such as uterine bleeding, severe nausea, vomiting, and weakness, which might require prompt medical intervention. For your information, I am enclosing an updated copy of the import alert, dated June 6, 1989, which instructs our field personnel to prevent the importation of unapproved abortifacient drugs such as RU-486.

I hope this information is helpful. If we can be of any further assistance, please let us know. A similar letter has been sent to the other co-signers of your letter.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

cc: All copies with copy of incoming and enclosure:

| | |
|---|---|
| HF-1 | HFW-10(2) |
| HF-2 | HFW-12 |
| HF-40 | HFW-1 |
| HF-43 | HFW-2 |
| | HFC-3 |

R/D: ——— (from previous approved corres.):5/18/89
R/T:itj:5/19/89:( —— ABORTIFACIENT)
F/D:itj:5/29/89:( —— ABORTIFACIENT)
Init: ——— :5/25/89
Init: ——:5/31/89
Edited: —— :6/31/89
Init: ——— :5/31/89
Init: —— :5/31/89
Retype:itj:6/8/89
F/T:itj:6/12/89

APPEARS THIS WAY
ON ORIGINAL

ROBERT K. DORNAN
38TH DISTRICT, CALIFORNIA

INTELLIGENCE COMMITTEE

ARMED SERVICES COMMITTEE
SUBCOMMITTEES:
COMBAT READINESS
RESEARCH AND DEVELOPMENT

SELECT COMMITTEE ON
NARCOTICS ABUSE AND CONTROL

PERMANENT OBSERVER TO
GENEVA ARMS TALKS

# Congress of the United States
## House of Representatives

CHAIRMAN
HOUSE REPUBLICAN STUDY
COMMITTEE

CHAIRMAN
RSC TASK FORCE ON
FOREIGN AFFAIRS

EXECUTIVE COMMITTEE
HOUSE REPUBLICAN RESEARCH
COMMITTEE

TASK FORCES:
AMERICANS MISSING IN ACTION
BUDGET REFORM
INTERNATIONAL NARCOTICS CONTROL
DEFENSE HIGH TECHNOLOGY
HISPANIC CAUCUS
GRACE COMMISSION CAUCUS

May 5, 1989

Honorable Frank Young, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Young:

An article published in the December 1988 issue of American Health, entitled "Mail Order Drugs from Abroad," asserts that you have approved a policy that would allow American citizens to mail order non-approved drugs from overseas for personal use.

While this apparent blanket policy is prima facie disturbing overall, one specific concern is that the French abortifacient RU 486 is not one of the 40 drugs specifically excluded. We are aware of the September 26, 1988 memo signed by Burton I. Love but we have seen no official statement from you confirming the ban on RU 486.

The U.S. government should not be involved in abetting abortion. This includes regulations that would allow the use of abortifacients such as RU 486. But of equal importance, the FDA should look at the effects non-approved drugs may have on the health and welfare of U.S. citizens. RU 486 has more than a dozen "contra indications" which proscribe its use. If a woman does not meet certain criteria, than she risks serious complications. That is why in France and China, where it has been legalized, RU 486 can only be administered under direct medical supervision. How then could the FDA possibly allow it to be purchased through mail order?!

We would greatly appreciate a clarification on your policy. Does your policy directive allow the importation of RU-486 or similar non-approved abortifacient drugs? If it does, have abortifacients such as RU 486 been imported under your directive? Finally, are there regulations currently being drafted that would add abortifacients, and specifically RU 486, to the list of prohibited drugs?

We look forward to your prompt reply.

Sincerely,

Robert K. Dornan, M.C. Henry Hyde, M.C. John LaFalce, M.C.

WASHINGTON, DC OFFICE: 301 CANNON HOUSE OFFICE BUILDING, WASHINGTON, DC 20515, (202) 225-2965
DISTRICT OFFICE: 12387 LEWIS STREET, #203, GARDEN GROVE, CA 92640, (714) 971-9292

Michael De Wine, M.C. Duncan Hunter, M.C. Thomas Bliley, M.C.

Arlan Stangeland, M.C. Bill Dannemeyer, M.C. Chris Cox, M.C.

Vin Weber, M.C. Clyde C. Holloway, M.C.

WPMAIL -ECHO
MAIL IMPORT-ALERT 'IMPORT ALERT 66-47'

DATE: JUNE 6, 1989

FROM: DIRECTOR, DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT ALERT #66-47 "Automatic Detention of Abortifacient Drugs"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

(HFC-101)
INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)
OFFICE OF REGULATORY GUIDANCE (HFF-310)
(HFC-160)
(HFC-210)
(GCF-1)
OFFICE OF COMPLIANCE (HFF-300)
(HFD-300)
(HFV-230)
(HFZ-300)
FIELD PROGRAMS BRANCH (HFF-26)
(HFC-42)
(HFB-100)
(HFC-6)
OFFICE OF ENFORCEMENT (HFC-200)
(HFC-230)
(HFF-25)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
(HFY-50)
(HPB-CANADA)
(HFC-41)
(HFD-301)
(HFC-6)

* * * * CORRECTION TO PREVIOUS TRANSMISSION * * * *

* * * * NAME OF PRODUCT CHANGED TO RU486 * * * *

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drug that induces abortion)

PROBLEM : New Drug without NDA/Safety from unsupervised use (DRND/DRHL)

PRODUCT CODE : 66[][][][][]

PAC : 56008H

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

CHARGE : "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug without an effective new drug application (NDA) as required by Section 505(a)."

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

REASON FOR
ALERT : Questions have been raised about a new abortifacient product, RU486 or "Mifepristone", (Import Bulletin 66-B13 9/26/88) and whether the agency should use its discretion, pursuant to the Pilot Guidance for Release of Mail Importations (7/20/88), or otherwise, to allow its importation for personal use. FDA has concluded that unapproved products of this kind would be inappropriate for release under the personal importation policy. The intended use of such drugs could pose a risk to the safety of the user.

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

/s/

APPEARS THIS WAY
ON ORIGINAL

A.F. FILE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Honorable Benjamin A. Gilman
House of Representatives
Washington, D.C. 20515

JUN 09 1989

Dear Mr. Gilman:

This is in response to your inquiry of May 11, 1989, on behalf of _____, concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

cc: F/D
FILE
COPY

3 Enclosures
Constituent's Letter
"Clinical Testing . . . ."
"A Primer on New . . . "

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
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| | /S/ | 6/5/89 | | | | | | |

MIF 005483

April 25, 1989

Congressman Benjamin A. Gilman
c/o U.S. House of Representatives
Washington, D.C. 20510

Dear Congressman Gilman:

I am writing to urge you to oppose any attempts to restrict the Food and Drug Administration from further testing of the drug RU-486. This drug provides an alternative to surgical abortion. Although first trimester abortion is currently one of the safest surgical procedures performed in the United States, RU-486 decreases or eliminates many of the occasional complications which can occur with any kind of surgery.

American women ought to have access to the best possible health care, and this includes making sure the safest methods are available for all legal medical procedures. Please don't allow a vocal minority to deprive all women of advances in medical technology.

Sincerely,

BENJAMIN A. GILMAN
22D DISTRICT, NEW YORK

FOREIGN AFFAIRS COMMITTEE

SUBCOMMITTEES:
EUROPE AND MIDDLE EAST
(RANKING MINORITY MEMBER)
INTERNATIONAL OPERATIONS

POST OFFICE AND CIVIL SERVICE COMMITTEE
(RANKING MINORITY MEMBER)

SUBCOMMITTEE:
INVESTIGATIONS

SELECT COMMITTEE ON NARCOTICS ABUSE AND CONTROL

SELECT COMMITTEE ON HUNGER

VICE CHAIRMAN,
TASK FORCE ON
AMERICAN PRISONERS AND
MISSING IN SOUTHEAST ASIA

# Congress of the United States
## House of Representatives
## Washington, DC 20515-3222

May 11, 1989

Dr. Frank E. Young
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Young:

I have received the attached communication from my constituent, _____ regarding the testing of RU-486.

I would welcome your review and every consideration which can be given to this matter will be appreciated.

Please provide me with a report of your findings when your review has been completed and have the letter returned to me with your reply.

Thank you for your kind attention.

Sincerely,

BENJAMIN A. GILMAN
Member of Congress

BAG:epc

APPEARS THIS WAY
ON ORIGINAL

PLEASE REPLY TO:

☒ WASHINGTON OFFICE:
2185 RAYBURN BUILDING
WASHINGTON, DC 20515-3222
TELEPHONE: (202) 225-3776

☐ DISTRICT OFFICE:
44 EAST AVENUE
P.O. BOX 358
MIDDLETOWN, NY 10940-0358
TELEPHONE: (914) 343-6666

☐ DISTRICT OFFICE:
223 ROUTE 59
MONSEY, NY 10952-3498
TELEPHONE: (914) 357-9000

☐ DISTRICT OFFICE:
32 MAIN STREET
HASTINGS-ON-HUDSON,
NY 10706-1602
TELEPHONE: (914) 478-5550

A.F. 75-[illegible]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Honorable [illegible]
House of Representatives
Washington, D.C. 20515

MAY 23 1989

Dear Mr. Fascell:

This is in response to your inquiry of April 25, 1989, on behalf of your constituents who are concerned about the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure your constituents that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

2 Enclosures
Clinical Testing . . .
A Primer on New . . .

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

cc: HFW-10(2)
R/D: 5/17/89
F/T:crw:5/19/89:( -RU486)

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
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| HFW-10 | /S/ | 5/89 | | | | | | |
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FILE COPY

MIF 005486

★U.S.GPO:1988-0-213-052

DANTE B. FASCELL
19TH DISTRICT, FLORIDA

FOREIGN AFFAIRS COMMITTEE
CHAIRMAN

ARMS CONTROL, INTERNATIONAL
SECURITY AND SCIENCE SUBCOMMITTEE
CHAIRMAN

SELECT COMMITTEE ON NARCOTICS
ABUSE AND CONTROL
MEMBER

CHARLES R. O'REGAN
ADMINISTRATIVE ASSISTANT

COMMISSION ON SECURITY AND
COOPERATION IN EUROPE
MEMBER

NORTH ATLANTIC ASSEMBLY
CHAIRMAN
HOUSE DELEGATION

CANADA—UNITED STATES
INTERPARLIAMENTARY GROUP
MEMBER, U.S. DELEGATION

# Congress of the United States

## House of Representatives

## Washington, DC 20515

April 24, 1989

Mr. Hugh C. Cannon, Associate Commissioner
for Legislative Affairs
Food and Drug Administration
5600 Fisher's Lane, Room 1555
Rockville, Maryland 20857

Dear Mr. Cannon:

Enclosed are copies of correspondence from some of my constituents.

It would be greatly appreciated if you would accord the comments in the letters every consideration and provide me with a report on the matter.

Many thanks for your assistance.

Sincerely,

Dante B. Fascell

DANTE B. FASCELL
Member of Congress

DBF/BT

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DANTE B. FASCELL
19TH DISTRICT, FLORIDA

FOREIGN AFFAIRS COMMITTEE
CHAIRMAN

ARMS CONTROL, INTERNATIONAL
SECURITY AND SCIENCE SUBCOMMITTEE
CHAIRMAN

SELECT COMMITTEE ON NARCOTICS
ABUSE AND CONTROL
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ADMINISTRATIVE ASSISTANT

COMMISSION ON SECURITY AND
COOPERATION IN EUROPE
MEMBER

NORTH ATLANTIC ASSEMBLY
CHAIRMAN
HOUSE DELEGATION

CANADA—UNITED STATES
INTERPARLIAMENTARY GROUP
MEMBER, U.S. DELEGATION

# Congress of the United States

## House of Representatives

## Washington, DC 20515

April 26, 1989

Mr. Hugh C. Cannon, Associate Commissioner
for Legislative Affairs
Food and Drug Administration
5600 Fisher's Lane, Room 1555
Rockville, Maryland 20857

Dear Mr. Cannon:

Enclosed are copies of correspondence from some of my constituents.

It would be greatly appreciated if you would accord the comments in the letters every consideration and provide me with a report on the matter.

Many thanks for your assistance.

Sincerely,

Dante Fascell

DANTE B. FASCELL
Member of Congress

DBF/BT

Enclosure

APPEARS THIS WAY
ON ORIGINAL

MIF 005488

DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Honorable Brock Adams
United States Senate
Washington, D.C. 20510

MAY 23 1989

Dear Senator Adams:

This is in response to your inquiry of April 24, 1989, on behalf of _____ concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

3 Enclosures
Constituent's ltr
Clinical Testing . . .
A Primer on New

cc: HFW-10(2)
R/D: 5/17/89
F/T:crw:5/19/89:( -RU486)

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| HFW-2 | FST | 5/22 | | | | | | |
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FILE COPY

MIF 005489

*U.S.GPO:1988-0-213-052

FDA

April 3, 1989

Dear Senator Adams -

I am writing to urge you oppose any attempts to restrict the Food and Drug Administration from further testing of the drug RU-486. This drug provides an alternative to surgical abortion. Although first trimester abortion is currently one of the safest surgical procedures performed in the United States, RU-486 decreases or eliminates many of the occasional complications which can occur with any kind of surgery.

American women ought to have access to the best possible health care, and this includes making sure the safest methods are available for all legal medical procedures. Please do not allow a vocal minority to deprive all women of advances in medical technology.

As for surgical abortion, keep it safe and legal - for all women, not only the wealthy.

Sincerely,

MIF 005490

BROCK ADAMS
WASHINGTON

COMMITTEES:
APPROPRIATIONS
LABOR AND HUMAN RESOURCES
RULES AND ADMINISTRATION

# United States Senate

WASHINGTON, D.C. 20510

April 24, 1989

Food and Drug Administration
Hugh C. Cannon
1555 Park Lawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Cannon:

Enclosed please find a copy of a request from my constituent, _____,

I would appreciate it if you could address my constituent's inquiries concerning her support for the drug RU-486.

Thank you for your attention to this matter. I look forward to your response.

Sincerely,

Brock Adams

BROCK ADAMS
United States Senator

BA/mk
Enclosure

APPEARS THIS WAY
ON ORIGINAL

# United States Senate

WASHINGTON, D.C. 20510

April 28, 1989

Director of Legislative Affairs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Sir:

Enclosed is correspondence that I have received from _____ concerning the drug RU-486. I would appreciate your expeditious attention to this matter.

Please respond directly to _____ However, for record purposes, please send a copy of your response to Janet McCracken of my staff.

Best regards.

Sincerely,

John Glenn

John Glenn
United States Senator

JG/jmm
Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MAY 02 1989

The Honorable Jesse Helms
United States Senate
Washington, D.C. 20510

Dear Senator Helms:

This is in further response to your February 23, 1989, inquiry relating to the Food and Drug Administration's (FDA) policy on the importation of unapproved drugs into the United States. Specifically, you asked whether citizens and companies would be allowed to import the drug RU-486 (mifeprisone), which is not approved for marketing in the United States.

For many years FDA has, as a matter of discretion, permitted individuals to bring into the United States, for their personal use, quantities of drugs sold abroad but not approved in the United States. Personal use quantities are generally considered to be amounts for a patient's treatment for three months or less. Imports involving larger quantities are generally not permitted as they could lead to commercialization.

As you know, in July 1988, the Agency issued written guidance to our field offices to clarify the policy's applicability to mail imports, and to ensure that our policies and practices in this important area are consistent throughout the country. The guidance states that unapproved drugs may be imported if there is no unreasonable safety risk or evidence of fraud, and other criteria are met relating to personal use, quantity, etc.

We do not believe that this policy can be appropriately applied to the importation of RU-486 because use of the product could present an unreasonable safety risk. That is, the intended use of this drug makes it likely it would be used without benefit of supervision of a physician and indiscriminate or unsupervised use could be hazardous to the patient's health. This is because the drug has potential side effects such as uterine bleeding, severe nausea, vomiting, and weakness, which might require prompt medical intervention. Copies of our July 20, 1988 guidance and an import bulletin on RU-486 dated September 26, 1988 are enclosed for your information. Please note that this bulletin prevents to the best of our ability RU-486 from entering the country for safety reasons.

FILE COPY

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*U.S. GPO: 1988-216-488

MIF 005493

I hope this information is helpful. If I can be of any further assistance, please do not hesitate to contact me.

Sincerely yours,

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

cc:
HFD-500( ) HFD- HFD
:3/16/89)
Concurrences. :3/16/89, :3/17/89
:3/17/89
Revised: :jmb:3/20/89
Init: :3/20/89
3/23/89
:3/24/89
Edit :3/24/89
R/T:vaj:3/24/89( 'RU-486)
R/T:car:3/30/89
Revised: :3/30/89
:3/30/89
with correction/addition :4/3/89
Re/T:car:4/3/89:
Edit: 4/3/89
Re/T:car:4/3/89
Edit: :4/10/89
Revise to include potential side effects: 4/12/89
Re/T:car:4/12/89
Revised: 4/12/89
Re/T:vaj:4/13/89
Edit: 4/13/89
:4/13/89
Init: 4/13/89
:4/13/89
4/14/89
Revised: :4/27/89
Init: :4/28/89
4/28/89
5/1/89
5/2/89
Revised: :5/2/89
F/T:vaj:5/4/89

APPEARS THIS WAY
ON ORIGINAL

JESSE HELMS
NORTH CAROLINA

# United States Senate

WASHINGTON, DC 20510

February 23, 1989

Mr. Frank E. Young, M.D. Ph.D.
Commissioner
Food and Drug Adminstration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Young:

It is my understanding that the FDA has issued a new policy allowing the importation of certain drugs currently unapproved by the FDA.

Under this new policy, will citizens and companies be allowed to import RU-486?

Kindest regards.

Sincerely,

Jesse Helms

JESSE HELMS:mjc

APPEARS THIS WAY
ON ORIGINAL

A F 93-253 FILE
Rouse C
MAY 01 1989

The Honorable Clarence E. Miller
House of Representatives
Washington, D.C. 20515

Dear Mr. Miller:

This is in response to your inquiry of March 30, 1989, on behalf of _____ concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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We are enclosing reprints, "Clinical Testing for Safe and Effective Drugs" and "A Primer On New Drug Development," that describe in more detail the requirements for new drug clearance in the United States.

We are unable to predict whether, or when, RU-486 will be approved for marketing. You may assure _____ that all important new drug submissions to FDA are given prompt attention, so that the public can benefit from new products as soon as possible.

FILE COPY

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*U.S. GPO: 1988-216-488

MIF 005496

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

2 Enclosures
Clinical Testing . . .
A Primer on New . . .

cc: HFW-10(2)
F/D: [redacted] :4/20/89
F/T:vaj:4/25/89:( [redacted] RU486)
Re/T: vaj:4/27/89

APPEARS THIS WAY
ON ORIGINAL

HOUSE OF REPRESENTATIVES, U.S.
WASHINGTON, D.C.

March 30, 198 9

*Respectfully referred to*
Food and Drug Administration
Room 1555
5600 Fishers Lane
Rockville, MD 20857

Please find enclosed a recent communication received by our office.

I would appreciate any information or assistance you can provide us in this regard so that we may answer this correspondence.

Thank you.

Sincerely,

Clarence E. Miller
Member of Congress
2308 Rayburn House Office Bldg
Washington, D. C. 20515

P.S. Please send your response to the attention of Ms. James in my office Thank you.

APPEARS THIS WAY
ON ORIGINAL

A F [illegible] FILE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

APR 28 1989

The Honorable Sam Nunn
United States Senator
Suite 1700
75 Spring Street, S.W.
Atlanta, Georgia 30303

Dear Senator Nunn:

This is in response to your inquiry of April 6, 1989, on behalf of [redacted] concerning the unapproved new drug, RU-486.

The Federal Food, Drug, and Cosmetic Act, which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

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FILE COPY

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MIF 005499

*U.S. GPO: 1988-216-488

We hope these comments are helpful. If we can be of further service, please let us know.

Sincerely yours,

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

2 Enclosures
Clinical Testing . . .
A Primer on New . . .

cc: HFW-10(2)
F/D: [redacted] 4/20/89
F/T:vaj:4/25/89:[redacted]-RU486)

APPEARS THIS WAY
ON ORIGINAL