I have reviewed 5 C.F.R. § 2635.502 and have consulted with certain FDA officials. It is advisable that I refrain from participating in any official matter affecting the drug product mifepristone or other anti-progestin drug products being developed for an indication identical to that for which initial approval of mifepristone is being sought. As stated above, since the beginning of my employment with the FDA, I have voluntarily recused myself from participating in these matters and, until further notice, I will continue to recuse myself from participating in these matters unless authorized to do so by the agency designee.

In order to help ensure that I do not participate officially in these matters, I have taken or will take the following steps:

- I have instructed _____ to handle any particular matter involving specific parties that could come before me that would affect or involve as a party any representatives or agents of the current NDA sponsor for mifepristone who are working on or associated with this NDA. This includes any representatives or agents of the NDA sponsor's current or future licensee(s) for mifepristone. It also includes any sponsors (or their representatives or agents) of documents, submissions or applications to the FDA (e.g., INDs, NDAs, supplements) for other anti-progestin drug products being developed for an indication identical to that for which initial approval of mifepristone is being sought. I have arranged for you (_____) to serve as their supervisor for this matter.

- I have provided you _____ with a copy of this memorandum and have asked _____ to refer to you any matters they believe are covered by my commitment to recuse.

- I have advised my immediate subordinates of this recusal.

If you would prefer to select someone other than an individual under my general supervision to act in my stead, please notify me of your determination so that I might provide the appropriate information to my subordinates.

In order to ensure that this disqualification continues to be effective, I will take the following steps in the future:

- I will revise and update this memorandum whenever that is warranted by relevant changes such as in my covered relationships, the financial interests of a member of my household, the nature of my duties or other changed circumstances, and provide you, the person exercising my authority, with a copy.

- I will advise my immediate subordinates and colleagues of any such changes.

SEP 17 1996

MEMO TO FILE

Date: September 17, 1996

NDA: 20-687

Product: Mifepristone

Sponsor: Population Council

Submission date: March 16, 1996, Received: March 18, 1996

****

The review team has worked hard on this priority application and I agree with the recommendation that the application is approvable.

Chemistry and biopharmaceutics deficiencies, discipline-specific labeling modifications and Phase 4 agreements have been conveyed to the sponsor and are reiterated in the letter being forwarded to ——— for consideration.

——— Group Leader memorandum reviews several outstanding clinical issues which have been discussed with and will continue to be addressed by the sponsor.

Along with the specific items enumerated in the action letter, the sponsor is aware that further items/modifications will require consideration before an approval action would be recommended. These include:

1. Continued update of data from the US clinical trial of this regimen.

2. Appropriate labeling

Along with the modifications suggested in the action letter, we must also consider appropriate changes to the patient labeling once the prescribing information is adequately revised. We also have asked the Division of Drug Marketing, Advertising and Communications to comment on the acceptability of the patient information and will incorporate their comments as labeling discussions continue.

3. Drug Distribution System

I agree with [redacted] conclusion that, if the applicant's proposal for a voluntarily system of limited distribution appears adequate, the imposition of further restrictions would not be warranted. We look forward to receiving a more comprehensive description of the proposed distribution system prior to a final determination on this issue.

4. Phase 4 agreements

As in our letter of August 22nd, with several modifications after discussion with the sponsor on September 12th, the six areas of post-approval monitoring as described in the forwarded action letter have been considered and will be pursued by the applicant after an approval action (as confirmed by a September 16th telefacsimile from the Population Council).

5. Advisory Committee input

Finally, the Reproductive Health Drugs Advisory Committee, which considered this application at a July 19, 1996 meeting, hopes to have the opportunity to comment on modified proposed labeling before approval as well as have the ability to review the final US study results when submitted and we anticipate providing this information as available.

In conclusion, I concur with the review team that an "approvable" letter be communicated to the sponsor at this time for mifepristone 600 mg, followed by 400ug of misoprostol two days later (unless termination has occurred) for pregnancy termination in women whose duration of amenorrhea is no more than 49 days. As agreed by the sponsor, the Center for Drug Evaluation and Research and the Reproductive Health Drugs Advisory Committee, the safe and effective use of this regimen requires certain conditions of use as described in the labeling.

/S/ 9-17-96

Division of Reproductive and Urologic Drug Products
HFD-580

cc:
NDA 20-687
HFD-580

SEP 16 1996

Memorandum

NDA:	**20-687**
Drug and indication:	**Mifepristone for pregnancy termination**
Applicant:	**The Population Council**
Submission date:	**March 14, 1996**
Date of MO reviews:	**June 27, 1996 [NDA review (draft)]** **August 28, 1996 and August 29, 1996 (safety update reviews)**
Date of Memorandum:	**September 16, 1996**

In this application, the Population Council requests approval for a medical regimen for pregnancy termination in women whose duration of amenorrhea is no more than 49 days. The regimen consists of mifepristone 600 mg, followed by 400 μg of misoprostol two days later unless termination has occurred. The safety and efficacy of this regimen are supported by the results of two historically controlled clinical trials conducted in 2480 French women and sponsored by Roussel Laboratories, and by extensive foreign marketing experience. The results and implications of data in the original NDA submission and in subsequent safety updates have been adequately discussed in ——— excellent clinical reviews. I concur with the recommendation that this application is approvable.

Although the data support the safety and efficacy of this regimen, several outstanding clinical issues need to be addressed prior to approval or during phase IV (see below). Additionally, deficiencies in chemistry, manufacturing and controls (CMC), which are discussed in the CMC review (and will not be reiterated in this memorandum), require resolution prior to approval. Despite these deficiencies, an approvable action is recommended at this time because access to this regimen has important public health implications for women; extensive experience with this regimen in European markets suggests that tolerability is acceptable; and the applicant has demonstrated their commitment to address these deficiencies in a responsible and timely manner. Outstanding issues were discussed with the applicant in a meeting on September 12, 1996 and agreement was reached on how to approach their resolution.

Outstanding clinical issues may be summarized as follows:

1. Limited data on use of this regimen in the United States

The reviewed data represent foreign experience in controlled settings (clinical trials and restricted marketing). Safety and efficacy in the U.S. health care setting have not been established at this time, although analysis of U.S. Population Council-sponsored studies is nearing completion. Reassuringly, preliminary analyses of the rate of serious adverse events in

these studies, presented at the July 19, 1996 meeting of the Reproductive Health Drugs Advisory Committee, were similar to experience in French trials and suggest that foreign safety data are generalizable to U.S. women treated in controlled settings. The sponsor has committed to submitting full study reports of the U.S. trials promptly after their completion. An executive summary of these results will be forwarded to Advisory Committee members and we anticipate that the label will be revised to incorporate U.S. data at that time.

2. Professional and patient labeling

The clinical sections of the product labeling require extensive revision, as noted in the appended labeling review (Attachment 1). Of particular note, the label should provide practitioners with: a) information relevant to single dose use of misoprostol; b) quantitative information from clinical trials on the success rate and the risk of serious adverse experience with this regimen; and c) any available information on the teratogenic risk of this regimen in animals and humans. Revisions have also been requested that reflect labeling comments from members of the Reproductive Health Drugs Advisory Committee regarding lack of data in women excluded from clinical trials (such as those with chronic medical conditions, at extremes of age, or with a heavy smoking history).

Comments from the Division of Drug Advertising, Marketing and Communications on the Patient Package Insert are pending and will be forwarded to the applicant upon completion.

3. Drug distribution

The applicant has appropriately proposed that drug distribution be limited to licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, [redacted] who will attend educational seminars on the safe use of this regimen. Based on concerns raised at the July 19, 1996 Advisory Committee meeting, the applicant has revised the initial distribution proposal to eliminate plans for training physicians in surgical abortion.

However, while we concur with the concept of limiting drug distribution to credentialed providers, the adequacy of the proposed plan can not be fully evaluated at this time because sufficient information on its implementation has not been submitted. The applicant has acknowledged this deficiency and has agreed to submit a comprehensive description of the distribution system for review, when available. Further, because the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted.

4. Phase IV commitments

Members of the Reproductive Health Drugs Advisory Committee recommended that several issues be addressed during Phase IV. These issues were reiterated in a letter to the applicant on August 22, 1996, and discussed during the September 12, 1996 meeting. During this meeting, the applicant committed to pursue Phase 4 studies with the following objectives:

a. To monitor the adequacy of the distribution and credentialing system;
b. To follow-up on the outcome of a representative sample of women who have surgical abortion because of method failure;
c. To assess the long-term effects of multiple use of the regimen;
d. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not;
e. To study the safety and efficacy of the regimen in women under 18 years of age, over age 35, and in smokers; and
f. To ascertain the effect of the regimen on children born after treatment failure.

The review team members, including [redacted] should be congratulated for their excellent work on this priority application.

/S/

[redacted], HFD-580

cc:
NDA20-687
HFD-580/ [redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Attachment 1
Clinical Comments on Mifepristone Draft Package Insert
September 10, 1996 (Revised September 16, 1996)

****Comment: Please excerpt and incorporate sections from the approved label for misoprostol that are relevant for single dose use of misoprostol as part of this regimen.****

Black Box Warning
Please propose a black box that includes the following elements:

[redacted]

Clinical Pharmacology
Please include a concise description of studies -14 and -24 that includes:

a. the number of patients treated and the success rate for the subset of patients with a gestational age $\leq$ 49 days and who took $\leq$ 1 dose of misoprostol.
b. when complete expulsion occurred in these studies.
c. the success rate after mifepristone only.

Indication and Usage
1. Please revise paragraph three to read as follows:

[redacted]

2. Please omit the first sentence of paragraph 4 ([redacted]

3. Re: the sentence [redacted]
   a. Please modify the end of this sentence to read ". [redacted] .
   b. After this sentence, please add "see PRECAUTIONS".

Contraindications
1. Re: paragraph 2, sentence 1
Please revise this sentence to read ".. [redacted] .."

Warnings

1. Please number each of the 3 paragraphs and please precede each paragraph with the following subheaders:
    1. Bleeding
    2. Confirmation of pregnancy termination

2. Please revise the first paragraph (on bleeding) as follows:
    a. "Vaginal bleeding occurs in almost all patients during the treatment procedure. Bleeding was reported to last for 69 days in one patient."

    b. Please incorporate quantitative information on the frequency of heavy bleeding and the need for treatment of anemia (such as, frequencies of transfusion, and medical and surgical interventions). These frequencies should be based on studies -14 and -24 for women with a gestational age $\leq$ 49 days.

    c. Note: The statement that should be retained.

Precautions

General

1. Please revise the first sentence to state that administration should be by a physician who is trained in this procedure.

2. Please revise paragraph 3 as follows:
"There are no data on the safety and efficacy of [product name] in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia; or heavy smoking history. Women who are more than 35 years of age and who smoke at least 10 cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials with this product.

3. The last paragraph of this section should be omitted and replaced with the following statement: "The effectiveness of [product name] may be lower if misoprostol is administered more than two days after mifepristone administration."

Drug Interactions

In the last sentence, please provide examples of commonly used drugs known to cause enzyme induction ("...such as ...").

Pregnancy - Teratogenic effects
Please include a concise discussion of the available information from rabbit studies and from human experience.

Nursing mothers
Please revise this section as follows:
"It is not known whether "Trade name" (mifepristone) is excreted in human milk. However, many hormones with a similar chemical structure can enter human milk.

Pediatric Use
Please revise this sentence to read, "Safety and effectiveness in patients , years of age have not been established."

Adverse Reactions
1. In place of the narrative, please incorporate a table of adverse events with a frequency $\geq$ 1% based on the combined results of studies -14 and -24. Please tabulate ADE rates in separate columns for women who took mifepristone alone and those who took mifepristone in combination with one dose of misoprostol. Please limit this table to those women whose gestational age was $\leq$ 49 days.

2. Please revise the narrative portion to concisely discuss the more serious adverse events or the more frequent adverse events, only.

3. Please eliminate the reference to

How Supplied
Please make specific reference to your distribution system.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products

Memorandum

Date: 10 Sep. 1996

From: [redacted], HFD-580

Subject: Labeling deficiencies

To: NDA 20-687

The draft labeling in the original NDA submission was reviewed in Chemistry Review # 1 dated 20 June 1996 and it was noted that minor labeling changes might be necessary. Labeling deficiencies were not conveyed to the Applicant because it was considered likely that an Amendment would be submitted to correct some obvious omissions (e.g. the lack of a structure for mifepristone in the Description Section). However, no Amendments pertaining to the chemistry related sections of the labeling have been submitted. The purpose of this Memorandum is to identify labeling deficiencies to be conveyed to the Applicant.
In the Description section of the draft package insert, the chemical name of mifepristone should be corrected by replacing "B" with "β". The structure of mifepristone should also be included. In addition, missing information in the 'How Supplied ' section regarding imprinting and carton contents should be provided.

CONCLUSIONS AND RECOMMENDATIONS: Labeling: The Applicant should be requested to include the structure of mifepristone in the Description section of the Package Insert and to correct the chemical name of mifepristone by replacing "B" by "β". The missing information (regarding imprinting and carton contents) in the 'How Supplied' section should also be provided. In addition, the Applicant should be informed that if a Tradename is to be used to market the product, it must be submitted and approved prior to use.

cc: Orig. NDA 20-687
HFD 580/ Div. Files
HFD 580/ [redacted]
R/D initialed by:

Filename: [redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date June 20, 1996

From _____ (HFD-510)
Advisory Committee for Reproductive Health Drugs

Subject Notice of Scheduled Advisory Committee Meeting

To Committee Management Office (HFA-306)
Through: _____ Division of ~~Metabolism and Endocrine~~ Reproductive and Urologic Drug Products, HFD-580 /S/ 6-21-96
/S/ 6/21/96 Office of Drug Evaluation II, HFD-102

We have scheduled an advisory committee meeting as described below and request that a notice be published in the Federal Register as follows:

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

Date, time, and place. July 19, 1996, 9 a.m., FDA Technical Center, 16071 Industrial Drive, Gaithersburg, MD. Attenders should allow time to proceed through security procedures. Admission to the facility by public participants will available on a first come, first serve, basis, and will be limited to 200, the number of seats available to the public in the conference room.

Type of meeting and contact person. Open public hearing, July 19, 1996, 1:30 p.m. to 3:30 p.m., unless public participation does not last that long; open committee discussion, 9 a.m. to 5 p.m.; Philip A. Corfman, M.D., Center for Drug Evaluation and Research, HFD-510, Food and Drug Administration, Rm. 14B-04, 5600 Fishers Lane, Rockville, MD 20857, phone 301-443-3510, fax 301-443-9282, email ~~July~~ july19@cder.fda.~~19@cder.fda.gov~~. (please keep email add on one lin Information concerning the meeting is available from FDA Advisory Committee Information Hotline, 1-800-741-8138 (301-443-0572 in the Washington, DC area), Advisory Committee for Reproductive Health Drugs, code 12537.

5772

[redacted]

Please call the Hotline for information concerning any possible changes.

General function of the committee. The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational human drugs for use in the practice of obstetrics and gynecology, and related specialties.

Agenda--Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person in writing by mail, email, or fax no later than 5 p.m., EDT on July 12, 1996, with a brief statement of the general nature of the evidence or arguments they wish to present, the names, telephone numbers, and addresses of proposed speakers, and an indication of the approximate time required to make their comments. The time for presentations will be allotted equitably, and will depend on how many individuals give advance notice within the time indicated of their intention to speak. In the interest of time, the Agency may require persons with common interests to make joint presentations.

Open committee discussion. The committee will discuss the new drug application for mifepristone for the interruption for early pregnancy.

/S/

Philip A. Corfman, M.D.

MAY - 9 1996

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 5, 1996

FROM: _____ /S/ 5/7/96
CSO, DMEDP

SUBJECT: NDA 20-687 Clinical Audits

TO: _____
Division of Scientific Investigations, Office of Compliance, (HFD-344).

THROUGH: _____ /S/ 5/8/96
Division of Metabolism and Endocrine Drug Products (HFD-510),
ODE II

Attached please find the names and locations of the study sites which comprise the two pivotal trials for this NDA which is for a new molecular entity. We request that you conduct clinical audits of a selection of these sites as part of our review of this NDA.

ENCLOSURES

cc:
Orig. NDA
HFD-510
HFD-510/ _____
HFD-510/ _____ /4.17.96/n20687.mem
concurrence: _____ 4.19.96/5.8.96

MEMORANDUM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date .26 April 1996 (Friday)

From [redacted] and Team Leader for Fertility and Maternal Health Drugs

Subject NOTICE OF JULY MEETING

To Members of the Advisory Committee for Reproductive Health Drugs

Please note that the Committee is scheduled to meet for one day, on Friday, 19 July 1996, to consider a New Drug Application for mifepristone and misoprostol for the interruption of early pregnancy.

In order to obtain optimal Committee participation, both retiring members and individuals nominated for replacement will be invited.

The FDA committee management staff will call your office soon to confirm your participation in the meeting.

/S/

Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

* Please note that the meeting planned for June 28 is still scheduled. Confirmation of that meeting will be provided as soon as possible.

APPEARS THIS WAY
ON ORIGINAL

E

THE WHITE HOUSE

WASHINGTON

January 22, 1993

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

APPEARS THIS WAY
ON ORIGINAL

THE WHITE HOUSE

WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

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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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

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 immediately begin analysis of existing evidence to determine if sufficient data exist to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. If sufficient evidence does not exist, please take immediate steps to rescind this import alert.

In addition, the President has directed the Department 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. Please keep me informed of your progress.

Attachments

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES ~~Public Health Service~~

Office of the ~~Assistant Secretary for Health~~ Secretary
Washington DC 20201

To: Acting Assistant Secretary for Health

From: The Secretary

Subject: Importation of RU-486

In accordance with the attached memorandum from the President, please instruct the Food and Drug Administration to immediately begin analysis of existing evidence to determine if sufficient data exist to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption. If sufficient evidence does not exist, please take immediate steps to rescind this import alert.

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

Please proceed with all possible speed in these matters and keep me informed regarding your progress.

Donna E. Shalala, Ph.D.

Attachment

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 22 1992 /S/

FROM: [redacted], Division of Metabolism and Endocrine Drug Products (HFD-510)

SUBJECT: RU-486 IND Information Requested by Mr. Wyden/
Control HFD-8-7-22C

TO: [redacted] Office of Legislative Affairs, HFW-12
THROUGH: [redacted] HFD-500

As requested, an updated (since May 20, 1992) description of all INDs in effect (regardless of whether investigations are active or not) in HFD-510 follows. (When an IND is "in effect", administration of the drug is permitted.)

IND Number SPONSOR CONTACT NAME PHONE NUMBER (MOST RECENTLY REPORTED STUDY ACTIVITY)	INDICATION	TYPE	ANTICIPATED NDA
IND [redacted] Population Council CONTACT: [redacted]	Abortion	Commercial	Not planned

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NO ADDITIONAL RU 486 IND's HAVE BEEN RECEIVED.

Only ———— and ——— have commented on their inability to obtain supplies of RU 486.

APPEARS THIS WAY
ON ORIGINAL

The following INDs have been canceled, terminated, or withdrawn. These INDs were very unlikely to have provided adequate information for an NDA submission either because they never started or they were for the treatment of a single patient.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-8/ [redacted] HFD-8-7-22C
HFD-500/Central No.: HFD-8-7-22C
HFD-510/Uterine acting agents
HFD-510/ [redacted]
HFD-510/ [redacted] /7.22.92/
Concurrences: [redacted] /7/22/92

APPEARS THIS WAY
ON ORIGINAL

MAJORITY MEMBERS
RON WYDEN, OREGON
CHAIRMAN

[illegible]

103d Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
[illegible]

[illegible]

July 22, 1993

Dr. David Kessler, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Bethesda, Maryland 20857
Via Fax: (301) 443-2567

Dear Dr. Kessler:

Pursuant to our on-going inquiry into the actions of your agency involving the French drug RU 486, I request the following:

-- A complete list of all investigational new drug (IND) approvals granted by your agency to persons or institutions conducting clinical trials with RU 486.

-- A brief description of these trials, individually.

-- Your understanding regarding the status of these trials, individually (Is experimentation on-going? Do researchers currently have quantities of RU 486, or are they receiving the drug from the company?).

-- The name and telephone number of a contact person for each IND.

As I believe this information is readily available, and may have been recently collated and up-dated by your staff, I request that your response be telefaxed to my subcommittee staff by close-of-business, Thursday. Their number is (202) 225-[illegible].

Should you have any questions regarding this request, please don't hesitate to contact me, or Steve Jenning of the subcommittee staff at (202) 225-7797.

Thank you for your assistance in this matter.

Sincerely,

RON WYDEN
Chairman

MIF 001922

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 24, 1991

FROM: [redacted] Division of Metabolism and Endocrine Drug Products (HFD-510) /S/ 4/24/91

SUBJECT: Response to Question 6 and part of Question 5 in the 4/11/91 Letter from the Hon. Henry Waxman, Control No. CDER-9104-0552

TO: [redacted] (HFD-008)

THROUGH: [redacted] Office of Drug Evaluation II (HFD-500) /S/ 4/24/91

As requested, a response to Mr. Waxman's 4/11/91 letter to Commissioner Kessler regarding additional questions posed by his committee in follow-up to a March 13 hearing is provided here.

Exhibit A.

Question 5 (partial): **Is there a separate regulation for abortifacient drugs (per [redacted] statement)?** (Wyden)

Response: The Food and Drug Administration has no regulations specifically prohibiting the importation of abortifacient drugs, and there is no Import Alert for abortifacients other than RU 486. However, the U.S. Customs Service has regulations prohibiting the importation of abortifacient drugs (19 CFR 12.40(h)) or literature or advertisements concerning devices to produce unlawful abortions (19 CFR 145.51(a)(2) and 145.52) (regulations attached).

Question 6: **Would France make available the results of studies on drugs, e.g., RU-486?**

Response: We understand that data for RU 486, including data presented to the French government regulatory agency, are owned by the manufacturer, Roussel Uclaf. At this time, we have no reason to believe that Roussel Uclaf would make such data for RU 486 available or that the French regulatory agency would share relevant data with FDA.

Please contact [redacted] at [redacted] if you have further questions.

ATTACHMENTS

the Semiconductor Chip Protection Act of 1984 (17 U.S.C. 901 *et seq.*), if the owner of a mask work which is registered with the Copyright Office seeks to have Customs deny entry to any imported semiconductor chip products which infringe his rights in such mask work, the owner must obtain a court order enjoining, or an order of the U.S. International Trade Commission (USITC), under section 337, Tariff Act of 1930, as amended (19 U.S.C.1337), excluding, importation of such products. Exclusion orders issued by the USITC are enforceable by Customs under paragraph (b) of this section. Court orders or exclusion orders issued by the USITC shall be forwarded, for enforcement purposes, to the Director, Entry, Procedures and Penalties Division, U.S. Customs Service, Washington, DC 20229.

(2) The district director shall enforce any court order or USITC exclusion order based upon a mask work registration in accordance with the terms of such order. Court orders may require either denial of entry or the seizure of violative semiconductor chip products. Forfeiture proceedings in accordance with Part 162 of this chapter shall be instituted against any such products so seized.

(3) This regulation will be effective against all importers regardless of whether they have knowledge that their importations are in violation of the Semiconductor Chip Protection Act of 1984 (17 U.S.C. 901-904).

[T.D. 79-231, 44 FR 49247, Aug. 22, 1979, as amended by T.D. 84-213, 49 FR 41167, Oct. 19, 1984; T.D. 87-132, 52 FR 39221, Oct. 21, 1987]

§ 12.39a Registered patent owners; import survey.

(a) When the owner of a patent registered in the United States believes that merchandise is being imported into the United States which infringes such patent, an application for a survey to assist the patent owner in taking appropriate action may be made. The purpose of the survey is to provide the patent owner with the names and addresses of importers of merchandise which appears to infringe the registered patent.

(b) The application may be made by letter addressed to the Commissioner of Customs, U.S. Customs Service, Washington, D.C. 20229. It shall state the name and address of the patent owner; and if available, a description of the merchandise believed to infringe the registered patent and the country of manufacture of the merchandise. A certified copy of the patent registration issued by the Patent and Trademark Office showing ownership to be in the name as claimed, 3 additional copies of the patent registration for Customs files, and a check or money order to cover the fee prescribed by § 24.12(a)(3) of this chapter for the survey selected shall be submitted with the application.

(c) Surveys will be made for periods of 2, 4 or 6 months at the option of the applicant.

[T.D. 56137, 29 FR 4720, Apr. 2, 1964, as amended by T.D. 84-133, 49 FR 26571, June 28, 1984]

Immoral Articles

§ 12.40 Seizure; disposition of seized articles; reports to United States attorney.

(a) Any book, pamphlet, paper, writing, advertisement, circular, print, picture, or drawing containing any matter advocating or urging treason or insurrection against the United States or forcible resistance to any law of the United States, or containing any threat to take the life of or inflict bodily harm upon any person in the United States, seized under section 305, Tariff Act of 1930, shall be transmitted to the United States attorney for his consideration and action.

(b) Upon the seizure of articles or matter prohibited entry by section 305, Tariff Act of 1930 (with the exception of the matter described in paragraph (a) of this section), a notice of the seizure of such articles or matter shall be sent to the consignee or addressee.

(c) When articles of the class covered by paragraph (b) of this section are of small value and no criminal intent is apparent, a blank assent to forfeiture, Customs Form 4607, shall be sent with the notice of seizure.

Upon receipt of the assent to forfeiture duly executed, the articles shall be destroyed if not needed for official use and the case closed.

(d) In the case of a repeated offender or when the facts indicate that the importation was made deliberately with intent to evade the law, the facts and evidence shall be submitted to the United States attorney for consideration of prosecution of the offender as well as an action in rem under section 305 for condemnation of the articles.

(e) All cases in which articles have been seized pursuant to 19 U.S.C. 1305(a) should be referred to the U.S. Attorney, for possible institution of condemnation proceedings, within 4 days, but in no event more than 14 days, after the date of Customs initial examination. The referral to the U.S. Attorney should be initiated simultaneously with the mailing to the importer of the seizure notice and the assent to forfeiture form. If the importer declines to execute an assent to forfeiture of the articles other than those mentioned in paragraph (a) of this section and fails to submit, within 30 days after being notified of his privilege to do so, a petition under section 618, Tariff Act of 1930 (19 U.S.C. 1618), for remission of the forfeiture and permission to export the seized articles, then the U.S. Attorney, who has already received information concerning the seizure pursuant to this paragraph, may proceed with the condemnation action.

(f) If seizure is made of books or other articles which do not contain obscene matter but contain information or advertisements relative to means of causing unlawful abortion, the procedure outlined in paragraphs (b), (c), (d), and (e) of this section shall be followed.

(g) In any case when a book is seized as being obscene and the importer declines to execute an assent to forfeiture on the ground that the book is a classic, or of recognized and established literary or scientific merit, a petition addressed to the Secretary of the Treasury with evidence to support the claim may be filed by the importer for release of the book. Mere unsupported statements or allegations will not be considered. If the ruling is favorable, release of such book shall be made only to the ultimate consignee.

(h) Whenever it clearly appears from information, instructions, advertisements enclosed with or appearing on any drug or medicine or its immediate or other container, or otherwise that such drug or medicine is intended for inducing abortion, such drug or medicine shall be detained or seized.

[28 FR 14710, Dec. 31, 1963, as amended by T.D. 71-165, 36 FR 12209, June 29, 1971; T.D. 76-261, 41 FR 39022, Sept. 14, 1976; T.D. 82-145, 47 FR 35477, Aug. 16, 1982; T.D. 85-186, 50 FR 47207, Nov. 15, 1985]

§ 12.41 Prohibited films.

(a) Importers of films, shall certify on Customs Form 3291 that the imported films contain no obscene or immoral matter, nor any matter advocating or urging treason or insurrection against the United States or forcible resistance to any law of the United States, nor any threat to take the life or inflict bodily harm upon any person in the United States. When imported films are claimed to be free of duty as American goods returned, this certification may be made on Customs Form 3311 in the space designated "Remarks" in lieu of on Form 3291.

(b) Films exposed abroad by a foreign concern or individual shall be previewed by a qualified employee of the Customs Service before release. In case such films are imported as undeveloped negatives exposed abroad, the approximate number of feet shall be ascertained by weighing before they are allowed to be developed and printed and such film shall be previewed by a qualified employee of the Customs Service after having been developed and printed.

(c) Any objectionable film shall be detained pending instructions from Headquarters, U.S. Customs Service or a decision of the court as to its final disposition.

Merchandise Produced By Convict, Forced, or Indentured Labor

§ 12.42 Findings of Commissioner of Customs.

(a) If any district director or other principal Customs officer has reason to believe that any class of merchan-

RU 486: THE IMPORT BAN AND ITS EFFECT ON MEDICAL RESEARCH

HEARING

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND ENERGY

OF THE

COMMITTEE ON SMALL BUSINESS HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

SECOND SESSION

WASHINGTON, DC, NOVEMBER 19, 1990

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this just a coincidence, or are we letting Mr. Helms just write these decisions?

Mr. CHESEMORE. Mr. Chairman, I don't believe that we are letting Senator Helms determine what the policy is. As you know, I think the subcommittee has records that show we indeed started drafting this policy many months before this. As a matter of fact, as I mentioned, we issued an import bulletin in June 1988, and we also had our guidance in place in June 1988. The import alert really, I guess, went along with that guidance.

Chairman WYDEN. But the fact is that antiabortion groups, and Senators, and Members of Congress who were supportive felt that it was very unclear in early 1989 what the status was of RU 486. You all moved very, very fast to respond to their concerns. I said it was a land-speed record, and I think I am going to use it in instances where I want to have queries answered by FDA for——

Mr. CHESEMORE. Mr. Chairman, we try to respond properly to all Members of Congress.

Chairman WYDEN. You have never treated this Member unfairly, but nobody in our office has ever gotten a response within 30 days. Is it a coincidence that the language was substantially that of Senator Helms' letter?

Mr. CHESEMORE. I think, indeed, we go back to what was in our pilot guidance, Mr. Chairman, back in September 1988, and a number of the factors that I talked about that we indeed consider prior to the importation for personal use.

Also, at the time that we were writing to Senator Helms, I'm sorry—I don't have the response in front of me—but I know that we have always believed and concurred in what the AMA statement was, that indeed we would carefully consider any IND and new drug applications submitted to the agency based upon its merits.

Chairman WYDEN. Now, exhibit F, that is the issued import alert, dated June 6, 1989. One part of that alert has elicited some special concerns by medical researchers. Under instructions, the line reads, and I quote: "Automatically detain all shipments of unapproved abortifacient drugs," and the concern among medical researchers here, is that now we may be out beyond just RU 486. Could you tell the subcommittee how many drugs are encompassed in what seems to be a very sweeping action?

[Exhibits A through F, referred to above, may be found in the appendix.]

Mr. CHESEMORE. I think I mentioned earlier, Mr. Chairman, we have some 58 import alerts on various human drugs, if that responds to your question. Some of those are indeed unapproved in this country.

Chairman WYDEN. But how many abortifacient drugs? I mean, this statement says, "Automatically detain all shipments of unapproved abortifacient drugs." What are we talking about here beyond RU 486? I think this is important, and I would like to know specifically what abortifacient drugs we are talking about here.

Mr. CHESEMORE. I will ask Dr. Sobel to expand on my response. I'm aware of one other particular compound, something called tricosanthin compound Q that is used in China as an abortifacient.

We also have an import alert on it. The other drugs are other unapproved drugs, unless Dr. Sobel knows of other ones.

Dr. SOBEL. I don't know of any others, except as a part of a general category of abortifacient drugs with a separate regulation, but I don't know of any specific compounds, other than RU 486.

Chairman WYDEN. Wouldn't we be talking about possibly hundreds of drugs, because this could be any drug with abortifacient properties, couldn't it? I mean, it seems to be a very sweeping statement, and certainly touches on some of the concerns of our researchers, in that more and more we are going to be seeing drugs with multiple benefits. Doesn't this touch possibly on hundreds of drugs?

Mr. CHESEMORE. Mr. Chairman, again, if there is an IND established for a drug, we would not detain that product from coming into the country. It could go on to its research use.

Chairman WYDEN. Tell me if you all feel that the controls that Roussel-Uclaf has established for RU 486 are inadequate.

Mr. CHESEMORE. I'm not sure that we've even had an opportunity to evaluate those controls.

Chairman WYDEN. Dr. Sobel, I want to hear from you in just a second. But Mr. Chesemore, you have issued an importation ban on the grounds that it is a health hazard because this drug could get into the United States and not be supervised. But yet you tell us that you haven't even looked at, or analyzed what Roussel-Uclaf is doing. Now, how can that be even——

Mr. CHESEMORE. I'm sure that they have excellent controls in France. Our concern would be, is that product getting out of France somehow, and when it does, how is it coming into this country.

Chairman WYDEN. You have no evidence of that either.

Mr. CHESEMORE. Not at this time.

Chairman WYDEN. No evidence whatsoever.

Mr. CHESEMORE. No; apparently their controls are working quite well.

Chairman WYDEN. Dr. Sobel.

Dr. SOBEL. Their controls seem to be very good; they are very careful about making sure the drug doesn't get out. However, whether this will be an ongoing process, we don't know. The United Kingdom, Scandinavian countries, and I believe Holland, are planning approvals, so to base a decision at one point in time in one set of circumstances is difficult.

I agree with you. The chance for this drug getting loose from France, so to speak, would seem to me from what I've heard and from discussions with people who know how it's given, is very small. But I don't think that that's the purpose of the import alert; it's establishing a principle which can respond to changing conditions overseas. I mean, we can't regulate by the international telegraph. We have to say, we are justified in imposing that, even though we acknowledge the conditions in France are excellent for distribution.

Chairman WYDEN. But your point, Dr. Sobel, is not responsive to my concern. You are saying that things seem to be fairly well controlled in France.

Dr. SOBEL. Very well controlled.

the shipment and retained for Customs purposes.

[T.D. 78-394, 43 FR 49788, Oct. 25, 1978, as amended by T.D. 89-1, 53 FR 51263, Dec. 21, 1988]

Subpart E—Restricted and Prohibited Merchandise

§ 145.51 Articles prohibited by section 305, Tariff Act of 1930.

(a) *Types of articles.* Various articles, as described in section 305, Tariff Act of 1930, as amended (19 U.S.C. 1305), and in Part 12 of this chapter, are prohibited from importation. This prohibition includes the following types of articles:

(1) Obscene matter;

(2) Articles for causing unlawful abortion (see § 145.52 for the treatment of literature pertaining to such articles);

(3) Matter advocating treason or insurrection against the United States or forcible resistance to any law of the United States;

(4) Matter containing any threat to take the life of or inflict bodily harm upon any person in the United States; and

(5) Lottery matter.

(b) *Disposition of articles.* Mail found to contain lottery matter shall be disposed of by the Postal Service under the postal laws and regulations. Mail found to contain any of the other prohibited articles described in paragraphs (a)(1) through (a)(4) of this section shall be given appropriate treatment by Customs under the Customs laws and regulations (see § 12.40 of this chapter).

§ 145.52 Literature concerning devices for unlawful abortion.

Mail articles containing literature or advertisements concerning devices to produce unlawful abortions, are prohibited from the mails by 18 U.S.C. 1461, and shall be retained by, or delivered to, the Postal Service for disposition under the postal laws and regulations. If the Postal Service determines in any case that it is proper to release the material to the addressee, it shall be submitted for Customs treatment before delivery.

[T.D. 78-99, 43 FR 13061, Mar. 29, 1978, as amended by T.D. 78-102, 43 FR 14455, Apr. 6, 1978]

§ 145.53 Firearms and munitions of war.

Importations of firearms, munitions of war, and related articles are subject to the import permit requirements and other restrictions set forth in 27 CFR Parts 47, 178, 179.

[T.D. 73-135, 38 FR 13369, May 21, 1973, as amended by T.D. 78-329, 43 FR 43455, Sept. 26, 1978]

§ 145.54 Alcoholic beverages.

(a) *Nonmailable.* Alcoholic beverages are nonmailable, with certain exceptions (see 18 U.S.C. 1716 and the postal regulations), and when imported in the mails are subject to seizure and forfeiture under 18 U.S.C. 545.

(b) *Seizure.* When alcoholic beverages are received in the mails, they shall be seized, and the addressee shall be advised that they are subject to forfeiture and that he has a right to file a petition for their release (see Part 171 of this chapter).

(c) *Conditions for release.* If the district director is satisfied that there was no fraudulent intent involved, he may release the alcoholic beverages to the addressee upon the following conditions:

(1) Applicable duty and internal revenue tax shall be paid.

(2) The addressee shall comply with the alcoholic beverage laws of the State to which the shipment is destined.

(3) Any other conditions the district director may impose under his authority to remit or mitigate fines, penalties, and forfeitures shall be complied with.

(4) The addressee, his representative, or a common carrier shall pick up the merchandise at the Customs office where it is being held. Since the merchandise is nonmailable, it cannot be delivered by the Postal Service.

§ 145.55 Trademarks, trade names, and copyrights.

Merchandise bearing a trademark or trade name entitled to protection against imports, merchandise bearing a mark or name that copies or simulates such a trademark or trade name, and merchandise which is in violation of copyright law is subject to the restrictions and prohibitions set forth in Part 133 of this chapter.

§ 145.56 Foreign Assets Control.

Merchandise subject to regulations of the Office of Foreign Assets Control of the Treasury Department prohibiting or restricting entry of unlicensed importations of articles directly or indirectly from North Korea, North Vietnam, Cuba, or Rhodesia shall be detained until licensed or the question of its release, seizure, or other disposition has been determined under the Foreign Assets Control or Cuban Assets Control regulations (31 CFR Parts 500 and 515).

§ 145.57 Regulations of other agencies.

Certain types of plants and plant products, food, drugs, cosmetics, hazardous or caustic and corrosive substances, viruses, serums, and various harmful articles are subject to examination and clearance by appropriate agencies before release to the addressee (see Part 12 of this chapter).

§ 145.58 Other restricted and prohibited merchandise.

Other restrictions and prohibitions pertaining to certain types of imported merchandise are set forth in Part 12 of this chapter and are applicable to importations by mail.

§ 145.59 Seizures.

(a) *Articles prohibited and contrary to law.* All mail shipments containing articles the importation of which is prohibited, or articles imported into the United States in any manner contrary to law, shall be seized or detained as appropriate and held by Customs officers for appropriate treatment, except for certain articles which will be handled by the Postal Service as specified in §§ 145.51 and 145.52.

(b) *Notification of seizure or detention.* In all cases where articles are seized or detained by Customs officers, the addressee shall be notified of the seizure or detention, of the reason for such action, and, if appropriate, of his right to petition for relief (see Part 171 of this chapter).

Subpart F—Exportation by Mail

§ 145.71 Exportation from continuous Government custody.

(a) *Relief from duties.* Merchandise imported into the United States, unless nonmailable, may be exported by any class of mail without the payment of duties, if:

(1) The merchandise has remained continuously in the custody of the Government (Customs or postal authorities); and

(2) The mail articles containing such merchandise are inspected and mailed under Customs supervision.

(b) *Waiver of right to withdraw.* Waiver of the right to withdraw the mail article from the mails shall be endorsed on each mail article to be so exported and signed by the exporter.

(c) *Export entry or withdrawal required.* An export entry in accordance with § 18.25 of this chapter or a warehouse withdrawal for exportation in accordance with § 144.37 of this chapter, whichever is appropriate, shall be filed for merchandise being exported under this section, except for merchandise imported by mail which is either:

(1) Unclaimed or refused and being returned by the Postal Service to the country of origin as undeliverable mail; or

(2) For which a formal entry has not been filed and which is being remailed from continuous Customs or postal custody to Canada.

[T.D. 73-175, 38 FR 13369, May 21, 1973, as amended by T.D. 73-175, 38 FR 17470, July 2, 1973; T.D. 78-102, 43 FR 14455, Apr. 6, 1978]

§ 145.72 Delivery to Customs custody for exportation.

In certain cases where merchandise has not been in continuous Government custody, delivery to Customs custody is appropriate before exportation by mail, as set forth in the following sections of this chapter:

(a) Section 10.8 (articles exported for repairs or alterations).

(b) Section 10.9 (articles exported for processing).

(c) Section 148.33 (merchandise which was imported free of duty under

To: ———
From: ———

———here are some further comments on this issue contained in a memo to ———
I am also sending some pertinent material.

Total transmission including this cover sheet is 8 pages..

/S/

To: FAX number ———————

This transmission contains a correction of a date — 16 July, 1996 (not 1996) The previous memo had an error — "July 1996"

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 12-Oct-2000 08:14am
From:
Dept: HFD-005 WOC2 3051
Tel No:

TO:

Subject: todays W.Post

FYI - two stories. the first was above the fold on the front page
M

Chinese To Make RU-486 For U.S.

By Philip P. Pan
Washington Post Foreign Service
Thursday , October 12, 2000 ; Page A01

SHANGHAI, Oct. 11 The Hua Lian Pharmaceutical factory emerges from fields of sorghum and green onions an hour's drive south of downtown Shanghai. At quitting time, workers board company buses that take them back to the city. Others leave on bicycles, pedaling toward nearby villages along narrow lanes dotted with oxen.

Despite the tranquil appearance, the Hua Lian plant is a secret factory of sorts. Its name and location are shielded not by Chinese authorities, but by the U.S. Food and Drug Administration, which two weeks ago approved the sale of a product that workers here are preparing to churn out for the American market--the abortion drug RU-486.

Supporters of RU-486, which offers an alternative to surgical abortions, have for years sought a manufacturer to produce it for the U.S. market, ever since boycott threats by antiabortion activists led the drug's French developers to renounce U.S. production in 1992. For eight years, no pharmaceutical company would develop it for sale in the United States.

So when the FDA announced it had approved the sale of RU-486, it took the unprecedented step of refusing to disclose the name or location of the manufacturer, citing concerns about employee safety and security. The drug's U.S. distributor, Danco Laboratories, also refused to identify the firm.

But several Chinese officials and the head of a Bangkok-based foundation that has worked closely with the company confirmed today that Hua Lian Pharmaceutical Co. will produce the drug for the United States.

An FDA official in Washington declined to comment, citing the agency's position that it would not disclose the location of the manufacturing site. Danco said in a statement from its New York offices that the site was inspected by the FDA to make sure it met the agency's requirements but that it could not identify the plant or comment on its location because of a confidentiality agreement.

The fact that a state-owned company in China will be producing RU-486, or mifepristone, for U.S. consumers could become part of a debate over the drug in the United States. Told of the Chinese factory's role, U.S. antiabortion activists said they intend to question the safety and purity of Chinese pharmaceuticals and tie the drug to China's controversial one-child policy and human rights record.

Douglas Johnson, legislative director of the National Right to Life Committee, said his group found the news "very disturbing." He also criticized the FDA for its refusal to reveal that the manufacturer was in China, saying the agency's rationale was "highly implausible."

"They said they wanted to protect the company from violence or protests, but it's ludicrous to say that is an issue in China, where demonstrations aren't permitted," he added. "It's a public relations problem they want to avoid--they don't want the association with Chinese coercive abortion practices."

RU-486 has been a key ingredient in China's population control strategy for years. Of the estimated 10 million abortions performed annually in China, about half are carried out with RU-486, said Gao Ersheng, director of the Shanghai Institute of Planned Parenthood Research.

Hua Lian has been making RU-486 for at least nine years, one of three companies in China that manufacture the drug. Established in 1939 and nationalized after the 1949 Communist revolution, it is one of the largest pharmaceutical firms in China, according to its Web site.

With the help of the Rockefeller Foundation and the Bangkok-based Concept Foundation, the company has been working for three years to upgrade its equipment and retrain its staff to meet international standards in order to be permitted to export the drug.

The Concept Foundation was established by the World Health Organization and World Bank in 1989 to assist factories in developing countries to make medical products at low cost for Third World health agencies. The Rockefeller Foundation gave $2 million to the group in 1997 to help Hua Lian and China's state family planning agency upgrade the factory.

Joachim Oehler, who heads the Concept Foundation, said the goal was to enable Hua Lian to produce export-quality RU-486 to be used in China and elsewhere as an emergency contraceptive. He said the foundations knew that would also allow Hua Lian to export the drug to be used for inducing abortions, but that that was not their goal.

Oehler said FDA inspectors spent a week at the factory in July and agreed to allow Hua Lian to produce RU-486 in bulk amounts for export to the United States. The factory is not certified to export RU-486 in pill form, but Oehler said he expects it to meet those standards in three to five months.

In the meantime, he said, Hua Lian will send RU-486 in amounts of about 100 pounds to another factory that will make it into pills. He said he does not know the location of the other factory but assumes it is in the United States and does not know if other factories elsewhere might manufacture the drug for U.S. use.

"If you compare it with other manufacturers in China, they are among the tops in terms of their production standards," Oehler said of Hua Lian. "The factory is in very good shape. It would not have survived the FDA inspection otherwise."

The Hua Lian Pharmaceutical Co. denied multiple requests for interviews or a tour of the factory, as did its corporate parent, the Shanghai Pharmaceutical Group Corp. But Gao and three Hua Lian officials said the factory will be making RU-486 for export to the United States.

Oehler said it is unclear how much RU-486 the factory will produce annually, but he said it can manufacture at least half a ton a year, or enough to meet the entire world demand.

Neither abortion nor RU-486 is a subject of moral debate in China in the way it is in the United States.

During the first decades of Communist rule, government authorization was required to obtain an abortion, and it was often difficult to obtain, especially for unmarried women. As a result, women often sought abortions from illegal providers, who often prescribed various forms of folk medicine. In the 1970s, though, China began to adopt population control measures and the government changed its policy, allowing women to obtain abortions without government approval.

China began experimenting with RU-486 as early as 1983, participating in clinical trials with the World Health Organization. In 1988, along with France, it became one of the first countries to approve the drug. By the mid-1990s, the drug had become popular for women seeking an alternative to surgical abortion.

Gao, the director of the research institute, attributed the popularity of the drug in part to the fact that most surgical abortions in China are performed without anesthesia and are thus extremely painful. In addition, many Chinese women choose RU-486 because they fear that complications during surgical abortions might harm their ability to have children later, other experts said.

"RU-486 has given women more choices, and it's been beneficial to women's health. It has also helped us limit the growth of the population," Gao said.

He also said he was not surprised by the debate in the United States. "My feeling is that isn't should be opposed. But if you oppose abortion, I

understand. But you shouldn't oppose it just because it's made in China. That shouldn't matter at all."

Staff writer Marc Kaufman in Washington contributed to this report.

Drug's U.S. Marketer Remains Elusive

By Robert O'Harrow Jr.
Washington Post Staff Writer
Thursday , October 12, 2000 ; Page A18

NEW YORK When many pharmaceutical companies win federal approval to market a new drug, they rush out predictions of potential riches for investors. Not so with Danco Laboratories LLC.

"A lot of what we're about is not driven by the profit motive," explained Richard Hausknecht, medical director of the firm, which just received permission to market the abortion pill known as RU-486.

"I'm not in this to get rich, because it's not going to make me any money," said Hausknecht, who said he is paid by the hour for his part-time work at Danco. "Here's a chance to offer to American women a real new option, something that has been denied to them for political reasons for 15 years."

Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry. It has worked for years and spent millions of dollars to bring to market a drug that investors knew would immediately face intense resistance--and they feared possibly violent intervention--from people opposed to abortion.

Danco has only a handful of employees. For security reasons, company officials say, Danco's telephone number is unlisted and the details of its whereabouts are carefully guarded. Company officials will say only that Danco is housed in an ordinary suite of offices somewhere in midtown Manhattan.

They say Danco intends to make a profit eventually. Its immediate plan is to make RU-486 available in the United States within a month as an early alternative to surgical abortion. The cost of the procedure, which includes two drugs and three office visits, is expected to be about $300, around the same as a surgical abortion.

The company also intends to research the possibility that the drug could also be a treatment for ovarian cancer and other life-threatening ailments.

Food and Drug Administration officials agree that Danco is not the usual pharmaceutical company. The agency "followed all normal" procedures in approving the drug, including inspecting the manufacturing facilities, officials said. But regulators determined that information about the manufacturer was

confidential under statutes governing trade secrets and freedom of information.

FDA Commissioner Jane E. Henney said the agency broke with precedent by not publishing the names of the experts who reviewed RU-486 for the agency. In another first, it did not publish the name or location of the company that will manufacture the drug.

Some antiabortion activists fear that because of Danco's secretive approach, it will not be held accountable the way other drug companies have.

"This company seems rather clandestine and, I believe, suspicious," said Judie Brown, president of the American Life League, an antiabortion group based in Stafford, Va. "Women should be able to know immediately who the provider of a particular product is."

Danco has a close relationship with the Population Council, a nonprofit reproductive-rights group that sponsored the drug for approval. In 1994, the Population Council was given the rights to sell RU-486 by French drugmaker Roussel-Uclaf SA, which was put off by the controversy surrounding the drug in the United States.

The council, supported by the Buffett Foundation and others intent on making abortion more accessible, in turn gave Danco the rights to manufacture and distribute the drug.

According to records filed in Delaware on Feb. 7, Danco was formed in the Cayman Islands on July 25, 1995. On those papers, Hausknecht was listed as vice president--a formality, he said, that lasted only a week.

Apart from some basic facts, company officials are chary with details about Danco's structure, its investors and its plans.

The chief executive is Roy Karnovsky, a former marketing executive for the Merck Human Health Division of Merck & Co. Through a spokesman, he declined to discuss the company.

Medical director Hausknecht is an associate professor of obstetrics and gynecology at Mount Sinai School of Medicine in New York. He also serves on an advisory board for Planned Parenthood and was the medical director for Planned Parenthood of New York City.

Danco's director of public affairs is Heather M. O'Neill, who has helped prepare materials for FDA hearings about the drug. O'Neill, a graduate of Harvard University's John F. Kennedy School of Government, previously worked as a consultant at the Population Council.

O'Neill, who joined Danco in 1997, declined to provide the names of individual investors. But she acknowledged that supporters generally share the company's desire to make RU-486 available.

Instead of talking about company profits, she refers to its "project."

"Everyone here is committed to this project, to making Mifeprex [the trade name for RU-486] available to all women," she said. "We've been singleminded in our determination in making Mifeprex an option American woman can have."

"It's extremely unusual," Kevin Schulman, director of the Center for Clinical and Genetic Economics at the Duke Clinical Research Institute. "Only people who are truly dedicated to 'the cause' would have stuck with it. The unique thing here is how everybody [involved] has a shared vision."

O'Neill said the company may eventually try to market RU-486 abroad but has no plans to do so now. "We, I think, would be interested in looking at certain other countries around the world," she said.

She said the company will soon have a higher profile at medical conferences and will begin providing educational material on how to use the drug safely and effectively.

The fact the manufacturer is not named would not prevent someone from filing an RU-486-related lawsuit. The target would be Danco, O'Neill said. "Danco is responsible for all aspects of the drug's introduction into the United States, from FDA compliance to manufacturing, marketing and distribution," she said.

O'Neill acknowledged that crucial financial support over the past decade came from several foundations.

The Buffett Foundation, which was begun by investor Warren E. Buffett and places a strong emphasis on reproductive issues, made at least $2 million in interest-free loans to the Population Council, according to tax documents filed in 1995. That money was in turn used to conduct clinical trials of RU-486.

One of Danco's main backers has been the David and Lucile Packard Foundation, which lent Danco $10 million in 1998 to support approval and marketing of RU-486.

Sarah Clark, director of the Packard Foundation's Population Program, said her group and other Danco backers share an array of motivations for taking on responsibility for such a controversial drug.

"We're trying to make sure this choice is available and is not kept out for the wrong reasons," she said. If it were up to more profit-oriented drug companies alone, she added, RU-486 would probably not be on the market: "We wouldn't have to make loans to Danco if the commercial market were there."

Electronic Mail Message

Date: 10/12/00 11:05:21 AM
From:
To: See Below
Subject: FWD: Press on Mifepristone

FYI

To:
To:
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To:
To:
To:

Electronic Mail Message

Date: 10/12/00 10:19:26 AM
From: [redacted]
Subject: Press on Mifepristone

You probably saw the story in the Washington Post or heard the news about the manufacturing site for mifepristone. The Agency's position continues to be, for all the reasons already stated, that we will not comment on the manufacturing site. If inquiries raise concerns about inspections, etc., we can certainly say that the manufacturing site for mifepristone received the same scrutiny as all manufacturing sites for all drugs but we can neither confirm nor deny the site. [redacted] will be discussing the FOI issues further with OCC.

[redacted]

Electronic Mail Message

Date: 10/11/00 4:20:37 PM
From:
To:
Cc:
Subject: Re: FOI Requests for Records - RU 486

MIME-Version: 1.0
Content-type: text/plain; charset=windows-1252

Content-transfer-encoding: 7BIT

The document request system can be searched on any of the fields in the request form. The two most likely places are in the title of the request (as specified by the requestor) and the title of the article or reference.

Attached is the result of looking in both of those fields for the terms that were provided as examples. If additional terms are needed, let me know or, , you can modify and run the query (also attached).

-----Original Message-----

Can you answer question?

Thanks

Electronic Mail Message

Date: 10/5/00 9:58:17 AM
From:
To:
Cc:
Cc:
Cc:
Cc:
Subject: FOI Requests for Records - RU 486

The FDA has received several Freedom of Information Act (FOIA) requests for documents related to RU-486, mifepristone, Mifeprex, or NDA 20-687. Each office, division, or organizational unit in CDER must review all files in its possession, custody, or control for any documents which refer or relate to any of these terms. Additionally, each CDER employee must search his/her personal files, including e-mails, for any such documents. Records that are responsive to the FOIA requests might include, but are not limited to, division files, personal files, e-mail correspondence (personal and divisional), memoranda, handwritten notes, and documentation of telecons. The all-subscriber e-mail of last week does not need to be submitted. No documents relating to any of the identified terms should be destroyed at this time.

Please send copies (not the originals) of all documents, with a cover page or note indicating the sender, to _____ in HFD-205 for evaluation. Email records should be sent in hard copy, not forwarded electronically. You should send copies of all identified documents, regardless of whether or not you believe a document is releasable. HFD-205 will review all of the documents to determine whether they are subject to release; sending a copy of a document to HFD-205 does not mean that the document will automatically be released.

We need copies of all documents by close of business on Friday, October 18, 2000. It is extremely important that we receive the copies by this time, so you should not wait until that afternoon to begin collecting them. Again, please retain the originals.

If you have any questions, please call _____

Electronic Mail Message

Date: 10/5/00 10:17:03 AM
From:
To:
Cc:
Cc:
Cc:
Subject: FWD: FOI Requests for Records - RU 486

If a document is already in the action package for mifepristone (RU486) and we have an identical copy of it in our files, do we need to provide the document again? Please note that FOI already has a copy of the action package.

Thanks,

From:
Sent: Thursday, October 05, 2000 5:57 PM
To: Hennev, Jane
Cc:
Subject: RE: Proposed Legislation on Mifepristone

FYI

Rep. Coburn did introduce the attached legislation on October 4 as HR 5385. He had 43 co-sponosrs

---Original Message---
From:
Sent:
To:
Cc:
Subject: Proposed Legislation on Mifepristone
Importance: High

Please find attached what we believe to be the legislation proposed by Rep. Coburn on limiting access to mifepristone. We have been told this is the proposal, however, we are not certain it has been filed yet and will not know until Thursday. Also below is language said to have been circulated by Rep. Coburn's office in suport of the legislation. If these versions change we will circulate new versions as soon as available.

<< File: coburn_095.pdf >>

> "COBURN OFFICE Summary of
> RU-486 Patient Health and Safety Protection Act
>
> The purpose of this bill is to protect mothers from the irresponsible and
> politically motivated malpractice of the Food and Drug Administration in
> approving this drug without safeguards. It is to ensure that RU-486 kills
> only one person at a time instead of two at a time.
>
> This bill simply codifies the patient protection standards that were
> reportedly considered by the FDA prior to approval of RU-486, but which
> were evidently dropped under political pressure from the abortion lobby.
>
> 1) The prescribing physician must be qualified to handle
> complication of an incomplete abortion. Basically, the prescribing
> physician must be able to do a dilation and curettage (d & c) in the event
> of an incomplete abortion. According to the clinical trials in the US,
> approximately 5% of the women who used this method of abortion prior to
> seven weeks LMP experienced an incomplete abortion. (Among the entire
> clinical trial population, which included those who had been pregnant
> longer, it was about 15%.) An incomplete abortion left untreated is a
> very serious, potentially fatal, complication.
>
> 2) The prescribing physician must be legally empowered to commit an
> abortion and trained to do so. The training standard is essentially the
> same as point 1; the legal standard is just current law.
>
> 3) The prescribing physician must be qualified to read a sonogram in
> order to date the pregnancy and identify an ectopic pregnancy. The
> effectiveness of RU-486 in killing the baby is sharply reduced after seven
> weeks, while the rate of complications is much higher. The use of RU-486
> in the case of an ectopic pregnancy is not recommended at all for the sake
> of the mother.

>
> 4) The prescribing physician must be properly trained in the
> administration of this drug. Doctors who don't know what they are doing
> are likely to hurt their patients.
>
> 5) The physician must have admitting privileges at a nearby
> hospital. Complications requiring emergency care, such as heavy bleeding,
> are relatively common with the use of this drug combination, and the
> prescribing physician must take responsibility for the care of his/her
> patients. If complications do arise, and the attending doctor is out of
> range or unavailable to care for his/her patient, other doctors who may
> have moral and ethical objections to abortion are then put in a position
> of having to perform the surgical abortion.
>
> The Coburn bill simply enacts these provision into law except for the
> provision creating a national registry of RU-486 providers and the
> provision calling for a follow-up study. Coburn believes these provisions
> should be left to the discretion of the Secretary of the Department of
> Health and Human Services."

Thanks

Electronic Mail Message

Date: 10/5/00 12:10:35 PM
From:
To: See Below
Subject: clarification on FOI request

I just talked to ~~~~ in FOI about the RU 486 FOI request. In order to avoid copying some documents multiple times she said the following would be acceptable. ~~~ would you willing to coordinate item 3 below? Also ~~~ would you please forward this message on to the others in 580 who need it-- thanks. ~~~

1. If you are certain that a document you have is a copy of one that is in the action package for mifepristone, you do not need to provide it again.

2. If you are not sure that a document you have is a copy of one that is in the action package, provide it.

3. If you are certain that you have a document that someone else also has, coordinate with that person and send the document only once. For example, I have the briefing notebook we put together for Dr. Henney. I plan to send that forward. There is no need to send additional copies of it. Before you decide someone else is providing the document and you don't have to send another copy check and be absolutely sure.

When in doubt, provide a copy!!!!!**

Electronic Mail Message

Date: 10/5/00 2:20:39 PM
From:
To:
Subject: FWD: Revulsion with Mifepristone Approval

Another RU-486 e mail. FYI I have collected all the e mails I received, including the ones I forwarded to you, re RU-486 for the FOI request, so you don't have to duplicate those.

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Oct-2000 05:47pm EDT
From:
Dept: HFD-230 PKLN 11B40
Tel No:

TO: See Below

Subject: RU 486 in Wednesday's New Mexican

"Health officials worried about RU-486" by Kristen Davenport. Santa Fe New Mexican, Wednesday, 10/4/2000. Talks about the differences between RU-486 and Emergency Contraceptive Pills (ECP), estrogen-progestin found in birth control pills and taken within the first 72 hours after unprotected sex. The ECPs are handed out in the about 50 Family Planning Public Clinics throughout New Mexico. [Not obvious from the headline] URL is http://www.sfnewmexican.com/health/index.las

Distribution:

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Electronic Mail Message

Date: 10/4/00 2:52:10 PM
From:
To:
Cc:
Cc:
Subject: FWD: Comments on Draft Response to Representative Tom Coburn's Letter of

comments.

Electronic Mail Message

Date: 10/4/00 2:51:20 PM
From:
Subject: Comments on Draft Response to Representative Tom Coburn's Letter of Sept

I have reviewed your draft response to Dr. Coburn's letter regarding misoprostol. Dr. Coburn is a family physician who has practiced obstetrics. I have no comments or clarifications to offer regarding your revisions. The revised draft response looks O.K. to me.

From:
Sent: Wednesday, October 04, 2000 7:07 PM
To: Hennev Jane;
Cc:
Subject: Proposed Legislation on Mifepristone
Importance: High

Please find attached what we believe to be the legislation proposed by Rep. Coburn on limiting access to mifepristone. We have been told this is the proposal, however, we are not certain it has been filed yet and will not know until Thursday. Also below is language said to have been circulated by Rep. Coburn's office in suport of the legislation. If these versions change we will circulate new versions as soon as available.

coburn_095.pdf

> "COBURN OFFICE Summary of
> RU-486 Patient Health and Safety Protection Act
>
> The purpose of this bill is to protect mothers from the irresponsible and
> politically motivated malpractice of the Food and Drug Administration in
> approving this drug without safeguards. It is to ensure that RU-486 kills
> only one person at a time instead of two at a time.
>
> This bill simply codifies the patient protection standards that were
> reportedly considered by the FDA prior to approval of RU-486, but which
> were evidently dropped under political pressure from the abortion lobby.
>
> 1) The prescribing physician must be qualified to handle
> complication of an incomplete abortion. Basically, the prescribing
> physician must be able to do a dilation and curettage (d & c) in the event
> of an incomplete abortion. According to the clinical trials in the US,
> approximately 5% of the women who used this method of abortion prior to
> seven weeks LMP experienced an incomplete abortion. (Among the entire
> clinical trial population, which included those who had been pregnant
> longer, it was about 15%.) An incomplete abortion left untreated is a
> very serious, potentially fatal, complication.
>
> 2) The prescribing physician must be legally empowered to commit an
> abortion and trained to do so. The training standard is essentially the
> same as point 1; the legal standard is just current law.
>
> 3) The prescribing physician must be qualified to read a sonogram in
> order to date the pregnancy and identify an ectopic pregnancy. The
> effectiveness of RU-486 in killing the baby is sharply reduced after seven
> weeks, while the rate of complications is much higher. The use of RU-486
> in the case of an ectopic pregnancy is not recommended at all for the sake
> of the mother.
>
> 4) The prescribing physician must be properly trained in the
> administration of this drug. Doctors who don't know what they are doing
> are likely to hurt their patients.
>
> 5) The physician must have admitting privileges at a nearby
> hospital. Complications requiring emergency care, such as heavy bleeding,
> are relatively common with the use of this drug combination, and the
> prescribing physician must take responsibility for the care of his/her
> patients. If complications do arise, and the attending doctor is out of
> range or unavailable to care for his/her patient, other doctors who may

> have moral and ethical objections to abortion are then put in a position
> of having to perform the surgical abortion.
>
> The Coburn bill simply enacts these provision into law except for the
> provision creating a national registry of RU-486 providers and the
> provision calling for a follow-up study. Coburn believes these provisions
> should be left to the discretion of the Secretary of the Department of
> Health and Human Services."

Thanks

.....
(Original Signature of Member)

106TH CONGRESS
2D SESSION

H. R. _____

IN THE HOUSE OF REPRESENTATIVES

Mr. COBURN introduced the following bill; which was referred to the Committee on _____

A BILL

To require the Food and Drug Administration to establish restrictions regarding the qualifications of physicians to prescribe the abortion drug commonly known as RU-486.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

October 3, 2000

SECTION 1. SHORT TITLE.

This Act may be cited as the "RU-486 Patient Health and Safety Protection Act".

SEC. 2. ESTABLISHMENT OF RESTRICTIONS REGARDING PRESCRIBING OF CERTAIN ABORTION DRUG.

With respect to the application that was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the drug mifepristone (commonly referred to as RU-486, to be marketed as MIFEPREX), and that was approved on September 28, 2000, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall promptly modify the conditions of the approval of such drug to establish the additional restriction that the drug may not be prescribed by any person other than a licensed physician who meets the following requirements:

(1) The physician is qualified to handle complications resulting from an incomplete abortion or ectopic pregnancy.

(2) The physician has been trained to perform surgical abortions and has met all applicable legal requirements to perform such abortions.

(3) The physician is certified for ultrasound dating of pregnancy and detecting ectopic pregnancy.

(4) The physician has completed a program regarding the prescribing of such drug that uses a curriculum approved by the Secretary.

(5) The physician has admitting privileges at a hospital to which the physician can travel in one hour or less, determined on the basis of starting at the principal medical office of the physician and traveling to the hospital, using the transportation means normally used by the physician to travel to the hospital, and under the average conditions of travel for the physician.

From: Jim Dickinson [ferdic@w3az.net]
Sent: Tuesday, October 03, 2000 12:50 PM
To:
Subject: Secret manufacturers


ATT44526.txt

In case it has slipped off your "scope," I'm presenting my emailed questions from Friday again, below. If what I've read is true, a precedent has been made here on "security" grounds in concealing the identity and location of a drug manufacturer that is supplying American consumers with products for which there are no quality, potency, identity, etc. criteria publicly available or reasonably accessible. For example, how does a requester identify for FOIA purposes the subject company and manufacturing site for which documentation (FDA-483, EIR, etc.) is sought?

Jim Dickinson (520-684-3112)

A public health and safety issue seems to have arisen in the secrecy FDA has afforded the name and address of the actual manufacturer of RU-486 (Mifeprex, mifepristone). If, as the Washington Post this morning suggests, the manufacturer is in China or India, and serious manufacturing issues arise, how is FDA able to quickly respond - especially since this is a drug with which there is little real-world experience in the U.S. and millions of American women will be suddenly exposed to it? We know from past experience that the first year of volume marketing is when the problems arise. With the actual manufacturer's identity and location being nonpublic, where is FDA's usual public accountability for drug quality in this case?

Jim

Electronic Mail Message

Date: 10/3/00 9:58:35 AM
From:
To: See Below
Subject: Re: verification of RU-486 reports

I concur.

FDA, CDER, OPDRA
12300 Twinbrook Parkway

Rockville, MD 20851 (HFD-400)

Electronic Mail Message

Date: 10/2/00 11:09:46 AM
From:
To:
Subject: FWD: Abortion Pill

The attached e mail concerns FDA policy on disclosure of manufacturing sites (pertaining to RU-486). Please respond with a cc to me.

Thanks.

Printed by [redacted]

Electronic Mail Message

Date: 02-Oct-2000 02:58pm
From: [redacted]
Dept: HFD-42 PKLN 17B17
Tel No: [redacted]

TO: [redacted]

Subject: final PI & MedGuide

[redacted]

I forgot to ask you, would you give a copy of the final MedGuide for Mifeprex to [redacted] & we need a copy of the final PI, if you didn't get one.

[redacted]

Printed by [redacted]

Electronic Mail Message

Date: 02-Oct-2000 11:04am
From: [redacted]
Dept: HFD-42 PKLN
Tel No: [redacted] FAX

17B17

[redacted]

TO: [redacted]

Subject: Danco website not in line with comments

[redacted]

The press release on the home page of the website has one of the originally proposed press releases.

I'm looking around the site now.

[redacted]

Electronic Mail Message

Date: 9/29/00 9:14:04 AM
From:
To:
Subject: Re: info this am please

Here's a brief chronology on Mifepristone (NDA 20687):

Receipt: 3/14/1996 Approval 9/28/2000

Total approval time = 54.4 months
(checking with PM to determine whether there is an adjustment)

Major milestones:

Receipt: 3/14/1996	Approvable: 9/18/1996
Major amendment: 8/18/1999	Approvable: 2/18/2000
Major amendment 3/30/2000	Approved: 9/28/2000

FDA Time = 18 months

Firm time = 36.4 months

Looks like the last cycle took 6 months.

Let me know if you need anything more or have questions. I'll bring up some background information for you.

>
>Could you please prepare for me the review statistics on the
>mifepristone application? Some Senator was talking this morning about
>how we had reviewed it in "just 6 months". Can't be the case! Could
>you please email me the submission date, actions dates, total FDA
review
>time, total response time, and total time to approval - so we have the
>information to refute such assertions. Please let me know if you have
>any questions about this,
>
>Many thanks
>

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Sep-2000 09:14am
From: [redacted]

Dept: HFD-023 WOC2 2040
Tel No: [redacted]

TO: [redacted]

Subject: Re: info this am please

[redacted]

Here's a brief chronology on Mifepristone (NDA 20687):

Receipt: 3/14/1996 Approval 9/28/2000

Total approval time = 54.4 months
(checking with PM to determine whether there is
an adjustment)

Major milestones:

Receipt: 3/14/1996	Approvable: 9/18/1996
Major amendment: 8/18/1999	Approvable: 2/18/2000
Major amendment 3/30/2000	Approved: 9/28/2000

FDA Time = 18 months

Firm time = 36.4 months

Looks like the last cycle took 6 months.

Let me know if you need anything more or have questions. I'll bring up some background information for you.

[redacted]

[redacted]

>
>Could you please prepare for me the review statistics on the
>mifepristone application? Some Senator was talking this morning about
>how we had reviewed it in "just 6 months". Can't be the case! Could
>you please email me the submission date, actions dates, total FDA
review
>time, total response time, and total time to approval - so we have the
>information to refute such assertions. Please let me know if you have
>any questions about this,
>
>Many thanks
>
[redacted]

Electronic Mail Message

Date: 09/29/2000 3:32:31 PM
From:
To:
To:
To:
To:
To:
Subject: Request

Office Heads:

Please forward the attached note to appropriate staffers that worked on the rollout.

Exec. Sec.

<<kudos.doc>>

Dear Colleagues,

I would like to personally thank each of you for your efforts in planning and conducting all aspects of the roll-out for the mifepristone approval. This team effort was critical in ensuring that the approval decision was communicated in a clear and timely manner to all interested parties. The conference calls with health professional and women's groups, the press interviews, the preparation of information for our Web site, and the calls, faxes, and e-mails to various other constituents resulted in delivery of a coordinated and coherent message regarding the approval. I appreciate the extra hours that some of you worked to make this happen. With an approval of this nature, which has engendered wide-ranging attention and equally wide-ranging reaction, I am grateful that together we have communicated the role of the FDA in a simple and forthright manner.

Jane E. Henney, M.D.
Commissioner of Food & Drugs

From: EXECSEC
Sent: Friday, September 29, 2000 3:32 PM
To:
Subject: Request

Office Heads:

Please forward the attached note to appropriate staffers that worked on the rollout.

Exec. Sec.


kudos doc

Dear Colleagues,

I would like to personally thank each of you for your efforts in planning and conducting all aspects of the roll-out for the mifepristone approval. This team effort was critical in ensuring that the approval decision was communicated in a clear and timely manner to all interested parties. The conference calls with health professional and women's groups, the press interviews, the preparation of information for our Web site, and the calls, faxes, and e-mails to various other constituents resulted in delivery of a coordinated and coherent message regarding the approval. I appreciate the extra hours that some of you worked to make this happen. With an approval of this nature, which has engendered wide-ranging attention and equally wide-ranging reaction, I am grateful that together we have communicated the role of the FDA in a simple and forthright manner.

Jane E. Henney, M.D.
Commissioner of Food & Drugs

Electronic Mail Message

Date: 9/28/00 1:25:57 PM
From:
To:
Cc:
Cc:
Cc:
Subject: NDA 20687: Mifeprex (Mifepristone) -

Can I assume this is a High Profile? will you want reports faxed?

FDA, CDER, OPDRA
12300 Twinbrook Parkway

Rockville, MD 20851 (HFD-400)

Phone

Electronic Mail Message

Date: 9/29/00 10:58:07 AM
From:
To:
To:
Cc:
Cc:
Subject: First Direct Report for RU-486

amazing?

FDA, CDER, OPDRA
12300 Twinbrook Parkway

Rockville, MD 20851 (HFD-400)

Phone

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Sep-2000 09:57am
From: [redacted]

Dept: HFD-580 PKLN 17B45
Tel No: [redacted]

TO [redacted]
TO: [redacted]

CC: [redacted]
CC: [redacted]
Subject: Label and Misc other files

If you have any problems with these files, call me.

[redacted]

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Sep-2000 11:18am
From: [redacted]
Dept: HFD-001 WOC2 6027
Tel No: [redacted] FAX [redacted]

TO: subscribers:

Subject: FWD: RU 486

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 9/28/00 12:04:00 PM
From:
To: See Below
Subject: Re: RU 486

Everyone, If you're still getting an error message, it's because you're browser has the old (wrong) address in memory. Please click on the refresh button to empty memory and then http://www.fda.gov/cder/drug/infopage/mifepristone should work.

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Electronic Mail Message

Date: 9/28/00 11:57:00 AM
From: [redacted] FAX [redacted]
To: See Below
Subject: Re: RU 486

I'm really sorry. I misspelled the drug name on the last message. The address should be http://www.fda.gov/cder/drug/infopage/mifepristone

It is correct on everything else but my message. [redacted]

Electronic Mail Message

Date: 9/28/00 11:53:00 AM
From: [redacted]
To: See Below
Subject: Re: RU 486

The web page is now live. http://www.fda.gov/cder/drug/infopage/mifespristone

Electronic Mail Message

Date: 9/28/00 3:30:50 PM
From:
To:
Cc:
Subject: FDA approval of RU-486

Hi Dr. Hammond,

I have been trying to contact you today to give you a heads up regarding the Agency's approval of RU-486. As I'm sure you are aware by now, this morning the agency approved the product.

We have created a website at which you can access the Agency's Press Release, the product's labeling, etc. The website is:

http://www.fda.gov/cder/drug/infopage/mifepristone

You can also call the Agency's drug information line: 1-888-463-6332 for information on the approval or if you have any questions. Of course, you can also contact me, and I will try to answer any questions that you may have.

If you have a better telephone and FAX number that we can use in the future, could you please pass that on to me.

Regards,

Advisors and Consultants Staff, HFD-21
FDA, CDER, ORM
5600 Fishers Lane
Rockville, Maryland 20857-1734

Electronic Mail Message

Date: 9/28/00 3:10:20 PM
From:
To:
To:
To:
To:
Subject: Re: Additional questions from reporters:

Additional questions from reporters:

Will Misoprostol be relabeled for this use? (reid)

It is up to Searle if it wishes to seek additional indications.

Are there any deaths associated with this regimen? (McCullough)

There were no deaths in the clinical trials in over 800 US patients and 1800 French patients.

When the label has a black box, what does that mean in terms of advertising restrictions? (Mccullough)

The contents in the box must be reflected in the ads and there are no reminder ads (ads that show drug name with no other words/writing).

Can we provide information on the issues raised in the last approvable letter issued to the company? (middleton)

See the web site for reviews for all cycles and outstanding issues idenfitied.

Electronic Mail Message

Date: 9/28/00 12:49:48 PM
From: [redacted]
To: [redacted]
To: [redacted]
To: [redacted]
Subject: Additional questions from reporters:

Additional questions from reporters:

Will Misoprostol be relabeled for this use? (reid)

Are there any deaths associated with this regimen? (McCullough)

When the label has a black box, what does that mean in terms of advertising restrictions? (Mccullough)

Can we provide information on the issues raised in the last approvable letter issued to the company? (middleton)

Electronic Mail Message

Date: 9/28/00 11:17:10 AM
From:
To:
To:
Cc:
Cc:
Subject: Redaction of Approval Letter

Attached is the Approval Letter for MIFEPREX™. We have removed any names from the letter. Please review and respond with any further redaction.

Thank You.

Printed by [redacted]

Electronic Mail Message

Date: 28-Sep-2000 11:17am
From: [redacted]

Dept:
Tel No:

Subject: RU 486

Greetings!

This is to let you know that FDA has just announced the approval of the drug, MIFEPREX (mifepristone), for terminating a pregnancy in the early stages (49 days or less since last menstrual period began). I have attached a copy of the press release for your information.

Agency staff have agreed on a comprehensive roll out strategy to communicate with all of our external audiences about this approval. If you or your staff receive inquiries, you may direct them to FDA's website, http://www.fda.gov/cder/drug/infopage/mifepristone <http://www.fda.gov/cder/drug/infopage/mifepristone> , or refer them to the designated contact below. The website contains the FDA press release, approval letter, package insert, medguide and other information on mifepristone. Please do not answer calls or emails directly.

Calls From:	Refer To:
Health Professionals/Consumers 888-INFO-FDA	OTCOM
301-827-4570 Print Media (Includes Trade Press) [redacted]	301-827-6250
[redacted] 301-827-6242 Broadcast Media 301-827-3417	[redacted]
Members of Congress/Staff 301-827-0087	[redacted]
Other Government Officials 301-827-4450	FDA Exec Sec

E-Mails should be forwarded to: druginfo@cder.fda.gov <mailto:druginfo@cder.fda.gov>

Please forward this information to anyone else on your staff who may receive inquiries.

Thanks,

[redacted]

Printed by [redacted]

Electronic Mail Message

Date: 28-Sep-2000 11:17am
From: [redacted]
Dept:
Tel No:

Subject: RU 486

Greetings!

This is to let you know that FDA has just announced the approval of the drug, MIFEPREX (mifepristone), for terminating a pregnancy in the early stages (49 days or less since last menstrual period began). I have attached a copy of the press release for your information.

Agency staff have agreed on a comprehensive roll out strategy to communicate with all of our external audiences about this approval. If you or your staff receive inquiries, you may direct them to FDA's website, http://www.fda.gov/cder/drug/infopage/mifepristone <http://www.fda.gov/cder/drug/infopage/mifepristone> , or refer them to the designated contact below. The website contains the FDA press release, approval letter, package insert, medguide and other information on mifepristone. Please do not answer calls or emails directly.

Calls From:	Refer To:
Health Professionals/Consumers 888-INFO-FDA	OTCOM
301-827-4570 Print Media (Includes Trade Press)	301-827-6250
[redacted] 301-827-6242	[redacted]
Broadcast Media 301-827-3417	[redacted]
Members of Congress/Staff 301-827-0087	
Other Government Officials 301-827-4450	FDA Exec Sec

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From: [redacted]
Subject: RU 486

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[redacted]

<<Miferpristone1.doc>>

P00-19
September 28, 2000
FOR IMMEDIATE RELEASE

FOOD AND DRUG ADMINISTRATION
Print Media: 301-827-6250
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

FDA APPROVES MIFEPRISTONE FOR THE TERMINATION OF EARLY PREGNANCY

The Food and Drug Administration today approved mifepristone (trade name Mifeprex) for the termination of early pregnancy, defined as 49 days or less, counting from the beginning of the last menstrual period.

Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin. Women will return for a follow-up visit approximately 14 days after taking mifepristone to determine whether the pregnancy has been terminated.

Because of the importance of adhering to this treatment regimen, each woman receiving mifepristone will be given a Medication Guide that clearly explains how to take the drug, who should avoid taking it, and what side

-More-

effects can occur.

"The approval of mifepristone is the result of the FDA's careful evaluation of the scientific evidence related to the safe and effective use of this drug," said Jane E. Henney, M.D., Commissioner of Food and Drugs. "The FDA's review and approval of this drug has adhered strictly to our legal mandate and mission as a science-based public health regulatory agency."

FDA based its approval of mifepristone on data from clinical trials in the United States and France.

The labeling for mifepristone emphasizes that most women using the product will experience some side effects, primarily cramping and bleeding. Bleeding and spotting typically last for between 9 and 16 days. In about one of 100 women, bleeding can be so heavy that a surgical procedure will be required to stop the bleeding.

The drug's labeling also warns that it should not be used in women with the following conditions:

- Confirmed or suspected ectopic ("tubal") pregnancies
- Intrauterine device (IUD) in place
- Chronic failure of the adrenal glands

-More-

- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
- Bleeding disorders or current anticoagulant (blood-thinning) therapy.

Under the terms of the approval, mifepristone will be distributed to physicians who can accurately determine the duration of a patient's pregnancy and detect an ectopic (or tubal) pregnancy. Physicians who prescribe mifepristone must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding -- or they must have made plans in advance to provide such care through others.

To gather additional data about the use of mifepristone, the Population Council (sponsor of the product) has made a commitment to conduct postmarketing studies. These include a study comparing patient outcomes among physicians who refer their patients needing surgical intervention, compared to those who perform surgical procedures themselves; an audit of prescribers that will examine whether patients and their physicians are signing the patient agreement and placing it in the patient's

medical record, as required; and a system for surveillance, reporting and tracking rare ongoing pregnancies after treatment with mifepristone in the U.S.

Mifepristone, which was developed by a French pharmaceutical firm, was first approved for use in France in 1988. Since then, more than 620,000 European women have taken mifepristone in combination with a prostaglandin to terminate pregnancy. The drug has also been approved in the United Kingdom, Sweden, and other countries.

Mifepristone will be distributed in the U.S. by Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at http://www.fda.gov/cder/drug/infopage/mifepristone/

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Danco Laboratories, LLC, New York, N.Y.

More detailed information about this product is available on FDA's website at

http://www.fda.gov/cder/drug/infopage/mifepristone/

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Electronic Mail Message

Date: 9/28/00 2:51:11 PM
From:
To:
Subject: As you requested

Electronic Mail Message

Date: 9/28/00 9:57:41 AM
From:
To:
To:
Cc:
Cc:
Subject: Label and Misc other files

If you have any problems with these files, call me.

Electronic Mail Message

Date: 9/28/00 10:07:39 AM
From:
To:
To:
Cc:
Cc:
Subject: AP Letter

Electronic Mail Message

Date: 9/28/00 10:24:09 AM
From:
To:
Cc:
Cc:
Subject: Approval Letter

Electronic Mail Message

Date: 9/28/00 11:11:08 AM
From: [redacted]
To: See Below
Subject: FWD: Redact Action Letter FDA names and [redacted] Memo of 9/

We need to make sure we've gotten the latest edited/redacted version of everything. Can someone come and help us review this [redacted]

Electronic Mail Message

Date: 9/28/00 10:48:21 AM
From: [redacted]
Subject: Redact Action Letter FDA names and [redacted] Memo of 9/28/00

As per our conversation,

The above two items are newly revised today and need redaction prior to placing on the web. Thanks.

[redacted]

Electronic Mail Message

Date: 9/28/00 8:52:19 AM
From: ARNOLD, SANDRA (SARNOLD@popcouncil.org)
To:
To:
Cc:
Cc: Nancy L. Buc Esq. (E-mail)
Subject: Revised documents

Attached are the package insert, including the MedGuide and Patient Agreement, and the prescribers agreement and order form, as submitted last night by fax.

<<FDALAB.9.27.2000.clean.doc>> <<Order-Prescriber Ltr 092700.doc>>

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Sep-2000 01:11pm
From: [redacted]
Dept: [redacted]
Tel No: [redacted]

TO: cder-migrated (cder-migrated@exchange.cder.fda.gov)
TO: All ALL-IN-1 users on this node (SUBSCRIBERS:)

Subject: FWD: RU 486

See attached for those of you already on Microsoft Outlook who did not get this the first time.

Electronic Mail Message

Date: 9/28/00 11:18:44 AM
From:
To: subscribers:
Subject: FWD: RU 486

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Sep-2000 11:18am
From: [redacted]

Dept: HFD-001
Tel No: [redacted] 6027

TO: subscribers:

Subject: FWD: RU 486

Printed by [redacted]

Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 28-Sep-2000 11:18am
From: [redacted]

Dept: [redacted] WOC2 6027
Tel No: [redacted]

TO: subscribers:

Subject: FWD: RU 486

From:
Sent: Thursday, September 28, 2000 12:14 PM
To:
Subject: FW: IMPORT ALERT #66-41

addendum has issued as well

-----Original Message-----
From:
Sent: Thursday, September 28, 2000 12:13 PM
To:
Subject: FW: IMPORT ALERT #66-41

FYI, also.

-----Original Message-----
From: ORA HQ DIOP Import Alerts
Sent: Thursday, September 28, 2000 12:02 PM
To:
Subject: IMPORT ALERT #66-41

DATE: SEPTEMBER 28, 2000

FROM: DIVISION OF IMPORT OPERATIONS & POLICY (HFC-170)

SUBJ: REVISION OF THE ATTACHMENT TO IMPORT ALERT #66-41, "UNAPPROVED NEW DRUGS PROMOTED IN THE U.S."

TO: IMPORT PROGRAM MANAGERS

The following product has met the criteria for detention without physical examination:

PRODUCT/ PRODUCT CODE	SOURCE	COUNTRY
Mifepristone 65J[][][][]/ 65D[][][][]	All	All

FDA has determined that unapproved versions of mifepristone manufactured outside the U.S. are being promoted in this country for use to end pregnancy. Due to the risks to the safety of the user in inadequately controlled settings, mifepristone should be considered inappropriate for release under the Personal Import Guidance. Districts encountering entries of mifepristone should determine whether the importer of record for the article being entered is Danco Laboratories, LLC, New York, New York (distributor of the U.S. approved product) or whether the article is being entered under an IND that is in effect. In such circumstances (when the article is being imported by the distributor of the U.S. approved product or under an IND that is in effect), the article is outside the scope of this guidance.

(Districts should contact CDER for verification of IND status.)

Please add this product to the attachment for Import Alert #66-41.

RECOMMENDED BY: DIOP (HFC-170)

FOI: No purging required

PREPARED BY: DIOP, Operations & Policy Branch

DATE LOADED

INTO FIARS: September 28, 2000

/s/