AGENDA

1. Measures to protect and inform patients
   a. Education by HHS/FDA
   b. Patient Information Leaflet
   c. Distribution requirements
   d. Consent form executed by patient
   e. Acceptance of terms executed by prescribing physician
   f. Definition of physicians who may prescribe
   g. Access to prostaglandin
   h. Measures against black market
   i. Monitoring of procedures and corrective actions.

2. The label
   a. Inclusion of items listed above
   b. Risks
   c. Indications and contraindications
   d. Treatment procedure
   e. Use of prostaglandin.

APPEARS THIS WAY
ON ORIGINAL

5010396.1

P

BEST POSSIBLE COPY

The Population Council

Approved Talking Points (23 September 1993)

1. Negotiations with Roussel Uclaf are still ongoing. We had expected we would have a signed agreement by mid-September, since many of the details granting the Council the license to bring RU 486 to the US have been worked out. The Population Council remains eager to complete the process and get on with our work.

2. The company re-raised issues recently that are beyond the capacity of the Council to resolve and that have therefore delayed completion of the contract. We do not think it would serve the purpose of getting agreement as quickly as possible to make public details of the negotiations at this delicate stage. We hope these difficulties can be overcome in the next week or two. The FDA and HHS were informed in early September that negotiations have been protracted.

3. The Population Council has taken a variety of actions in good faith reliance on Roussel's public commitment to grant us the license: we have prepared a protocol to amend our IND; negotiated with a management team and subcontractors to conduct a clinical trial; hired additional staff; developed and sent questionnaires to about 60 sites and investigators to help in selection of locations for the trial; amassed information about potential companies for manufacture and distribution and established criteria; worked on informational materials for providers and clients; and arranged for funding. The Council has gone about as far as we can go in making commitments without a signed contract.

—/9-23-93

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL

To

Dept./Agency FDA

Fax #

Phone #

Fax #

NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

READS THIS WAY
ORIGINAL

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

DATE: JUNE 6, 1989

FROM: [redacted], DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT ALERT [redacted] "Automatic Detention of Abortifacient Drugs"

TO : IMPORT PROGRAM MANAGERS

APPEARS THIS WAY
ON ORIGINAL

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

[redacted] (HFC-101)
INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)
OFFICE OF REGULATORY GUIDANCE (HFF-310)

[redacted] (HFC-160)
[redacted] (HFC-210)
[redacted] (GCF-1)
OFFICE OF COMPLIANCE (HFF-300)
[redacted] (HFD-300)
[redacted] (HFV-230)
[redacted] HFZ-300)
FIELD PROGRAMS BRANCH (HFF-26)
[redacted] (HFC-42)
[redacted] (HFB-100)
[redacted] (HFC-6)

OFFICE OF ENFORCEMENT (HFC-200)
[redacted] (HFC-230)
[redacted] (HFF-25)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
[redacted] (HFY-50)
[redacted] (HPB-CANADA)
[redacted] (HFC-41)
[redacted] (HFD-301)
[redacted] (HFC-6)

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

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

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drug that induces abortion)

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

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

PAC : 56008H

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

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

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

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

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

/s/

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

IMPORT ALERT

ORO/DFI (HFC-131)
IMPORT OPERATIONS BRANCH

Automatic Detention of Abortifacient Drugs

No.: 66-47 Revised
Date: April 17, 1990

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drugs that induce abortion)

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

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

PAC : 56008H

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

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

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

REASON FOR
ALERT : Questions have been raised about the abortifacient product, RU486 or "Mifepristone" (Import Bulletin 66-B13 9/26/88) and whether the agency should use its discretion, pursuant to the Regulatory Procedures Manual chapter 9-71, "Coverage of Personal Importations" (12/11/89), or otherwise, to allow its importation for personal use.

FDA has concluded that unapproved products of this kind would be inappropriate for release under the personal importation policy. The intended use of such drugs could pose a risk to the safety of the user.

RU-486 has also been called RU-38-486. Chemical names for RU-486 vary and are listed below:

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

2. 11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop-1-ynyl) -estra-4,9-dien-3-one

3. 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-estra-4,9-diene-3-one

4. 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-E

5. (11B,17B)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one

6. 11B-[4-(N,N-dimethylamino)phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

APPEARS THIS WAY
ON ORIGINAL

CHAPTER 9-71 COVERAGE OF PERSONAL IMPORTATIONS

9-71-00 Purpose
10 Background
20 Personal Baggage
25 Mail Shipments
30 General Guidance
40 Import Alerts

9-71-00 PURPOSE

To provide guidelines for the coverage of personal-use quantities of FDA-regulated imported products in baggage and mail and to gain the greatest degree of public protection with allotted resources.

9-71-10 BACKGROUND

This new chapter consolidates policy and procedures that previously existed in RPM Chapter 9-71, Mail Importations; RPM Chapter 9-72, Coverage of Importations Contained in Personal Baggage; and, Pilot Guidance for Release of Mail Importations.

Because the amount of merchandise imported into the United States in personal shipments is normally small, both in size and value, comprehensive coverage of these imports is normally not justified. Small shipments, however, are occasionally entered in baggage or mail as a way of avoiding formal entry review. This guidance clarifies how FDA may best protect consumers with a reasonable expenditure of resources.

There has always been a market in the United States for some foreign made products that are not available domestically. For example, individuals of differing ethnic backgrounds sometimes prefer products from their homeland or products labeled in their native language to products available in the United States. Other individuals seek medical treatments that are not available in this country. Drugs are sometimes mailed to this country in response to a prescription-like order to allow continuation of a therapy initiated abroad. With increasing international travel and world trade, we can anticipate that more people will purchase products abroad that may not be approved, may be health frauds, or may be otherwise not legal for sale in the United States.

In addition, FDA must be alert to foreign and domestic businesses that ship unapproved, fraudulent, or otherwise illegal medical treatments into the United States or who encourage persons to order these

products. Such treatments may be promoted to individuals who believe that treatments available abroad will be effective in the treatment of serious conditions such as AIDS or cancer. Because some countries do not regulate or restrict the commercial exportation of unapproved products, people who mail order from these businesses may not be afforded the protection of either foreign or U.S. laws. In view of the potential scale of such commercial operations, FDA has focused its enforcement resources more on products that are shipped commercially, including small shipments solicited by traditional mail-order promotions, and less on those products that are personally carried, shipped by a personal non-commercial representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

9-71-20 PERSONAL BAGGAGE

FDA personnel are not to examine personal baggage. This responsibility rests with the U.S. Customs Service. It is expected that a Customs officer will notify the local FDA district office by telephone when he or she has detected a promotional shipment or a shipment of an FDA-regulated article intended for commercial distribution (see 9-71-30), an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or an unknown risk to health.

When items in personal baggage are brought to FDA's attention, the district office should use its discretion, on a case-by-case basis, in accordance with the guidance provided in 9-71-30 in deciding whether to request a sample, detain the article, or take other appropriate action.

9-71-25 MAIL SHIPMENTS

Generally, FDA personnel only monitor mail importations. It is expected that a Customs officer from the Customs Mail Division will examine a parcel and will set it aside if it appears to contain a drug, biologic, or device, an article that FDA has specifically requested be detained, or an FDA-regulated article that represents a health fraud or unknown risk to health.

FDA should audit those parcels set aside by Customs in accordance with the guidance provided in 9-71-30 using the following procedures:

Complete the form FD-725 "Mail Collection Report" for each parcel collected for sampling. Generally, a physical sample is not required on mail importations because a documentary sample, e.g.,

labels, inserts, etc., will be sufficient for most regulatory purposes. If a physical sample is needed, collect only the minimum necessary for analysis by the laboratory. The remaining portion should not be removed from the custody of the Customs Mail Division.

Importations detained in accordance with this guidance should be held by Customs until they are either released or refused entry. Attached as guides are two specimen letters that may be sent with the Notice of Detention and Hearing when a parcel is detained: Exhibit X9-71-1 for use in general mail importations, and Exhibit X9-71-2 for use in unapproved drug or device mail importations.

On occasion, products detained by FDA will be mixed with non-FDA-regulated products. When we refuse admission of the FDA-regulated portion, any request for the release of the non-FDA-regulated portion should be referred to the Customs Mail Division with a Notice of Refusal of Admission covering the detained article. Final disposition of all merchandise, including the destruction of detained merchandise, is the responsibility of Customs.

9-71-30 GENERAL GUIDANCE

Even though all products that appear to be in violation of statutes administered by FDA are subject to refusal, FDA personnel may use their discretion to examine the background, risk, and purpose of the products before making a final decision. Although FDA may use its enforcement discretion to allow admission of certain violative items, this should not be interpreted as a license to individuals to bring in such shipments.

A. Commercial or Promotional Shipments

Commercial and promotional shipments are not subject to this guidance. Whether or not a shipment is commercial or promotional should be determined by a number of factors including the type of product, the accompanying literature, the size, value, and the destination of the shipment. FDA personnel should also consider whether an importation of drugs or medical devices is a commercial shipment by evaluating whether the article appears to have been purchased for personal use or whether the quantity suggests commercial distribution (i.e., the supply exceeds what one person might take in approximately three months). Commercial shipments include most shipments other than those products that are personally carried, shipped by a personal non-commercial

representative of a consignee, or shipped from a foreign medical facility where a person has undergone treatment.

B. Products Other than Drugs and Devices

Many products other than drugs, biologics, and devices that individuals seek to import in personal quantities do not pose a significant health risk, although they appear to be violative and may already be the subject of an import alert or automatic detention on the basis of filth or labeling problems. When such items are brought to FDA's attention by Customs, it may be appropriate for FDA personnel to use their discretion to "Release with Comment" and advise the importer of the agency's concerns. FDA personnel should be alert to, and should detain, however, those products that do pose a significant health risk, such as ackee or betel nuts.

C. Drugs, Biologics, and Devices

When personal shipments of drugs and devices that appear violative are brought to FDA's attention by Customs, FDA personnel will have to use their discretion to decide on a case by case basis whether to sample or detain. Generally, drugs and devices subject to Import Alerts are not amenable to this guidance. Devices to be used by practitioners for treating patients should not be viewed as personal importations subject to this chapter. Drugs subject to Drug Enforcement (DEA) jurisdiction should be returned to Customs for handling.

In deciding whether to exercise discretion to allow personal shipments of drug or devices, FDA personnel should consider a more permissive policy in the following situations:

- o when the intended use is appropriately identified, such use is not for treatment of a serious condition, and the product is not known to represent a significant health risk; or

- o when 1) the intended use is unapproved and for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means; 2) there is no known commercialization or promotion to persons residing in the U.S. by those involved in the distribution of the product at issue; 3) the product is considered not to represent an unreasonable risk; and 4) the individual seeking to import the product affirms in writing that it is for the patient's own use (generally not more than 3 month supply)

and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product or provides evidence that the product is for the continuation of a treatment begun in a foreign country.

Where there are any questions about the application of these factors to any product, the product should be detained and FDA personnel should consult with the appropriate headquarters office.

Where a shipment is not detained or refused, FDA personnel should "Release with Comment" and, as appropriate, advise the recipient that 1) the drug (or device) that has been obtained for personal use appears to be unapproved in the United States; 2) the drug (or device) should be used under medical supervision; 3) FDA may detain future shipments of this product; and 4) the patient's physician should consider enrolling the patient in an Investigational study or applying for an Investigational New Drug (IND) exemption.

9-71-40 IMPORT ALERTS

FDA personnel should recommend to HFC-131 the issuance of an import alert if they encounter:

- o personal importation of products that represent either a direct or indirect risk;
- o the promotion of unapproved foreign products for mail-order shipment; or
- o repeated importation of products that represent a health fraud.

APPEARS THIS WAY
ON ORIGINAL

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release

January 22, 1993

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

# # #

D

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, December 17, 1992

DEC 17 11 56 AM '92

Doctor David A. Kessler
Commissioner of Food and Drugs
Department of Health & Human Services
Food and Drug Administration
Rockville, MD 20857
USA

Dear Doctor Kessler,

Thank you very much for your recent letter concerning RU 486.

Indeed, we are perfectly aware that the change in the opinion of the American administration will modify considerably the status of the drug in the United-States.

I am also fully confident that in light of the considerable number of clinical trials on voluntary termination of pregnancy which were initiated many years ago, it should probably be possible for us to ask for an NDA.

Like me, you are, no doubt, aware of the numerous violent reactions which have been launched against RU 486 by pro-lifers. As a matter of fact, although we received thousands of signatures and petitions from these people, we received even more letters of support from pro-choice people.

Under these circumstances, it has appeared to me that it would be better to start clinical trials in the United States. There are many possibilities: through the Population Council, Family Planning organizations, by licensing-out to third parties... This, in order to give American scientists and clinicians the opportunity to experiment the drug and get a chance to make public statements on its many applications.

We are presently in the process of reviewing our strategy in this direction, and we should be able to come up with some proposals by the end of January. I would, then, be delighted to meet you in order to discuss the RU 486 issue in your country.

Yours sincerely,

92-8252

35, Boulevard des Invalides 75007 Paris

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 15, 1992

Representative Ron Wyden
Chairman
Subcommittee on Regulation,
Business Opportunities, and Energy
House of Representatives
B-363 Rayburn House Office Building
Washington, D.C. 20515-6318

Dear Mr. Wyden:

This is in response to your letter of December 10, 1992, regarding the drug mifepristone (RU-486) manufactured by Roussel-Uclaf, in which you ask several questions.

You asked first whether the Food and Drug Administration would consider clinical trials in Europe as adequate evidence of the drug's safety and efficacy for purposes of approval in the United States for interruption of early pregnancy and whether additional human testing might be necessary to fulfill United States requirements. As with any other drug, the FDA is willing to consider foreign clinical trials as evidence of safety and efficacy, although we always reserve the right to audit the data according to our usual procedures. We recently approved an oral contraceptive (Desogen) based entirely on clinical studies conducted in the United Kingdom. Other drugs have also been approved on the basis of foreign trials alone. Agency staff who will be responsible for reviewing any mifepristone application report that, based on publicly available information and literature reports, the available data may well be sufficient to permit an adequate review. Therefore, further clinical trials may not be required. However, without an application submitted to the Agency for review, we cannot give a definitive answer on this question.

You also ask for an estimate of the length of time and the costs involved for a company seeking to obtain approval of mifepristone in the United States. While we are not experts on cost issues, the costs of preparing a new drug application for this product should not be excessive because much of the necessary information is already available. The Pharmaceutical Manufacturers Association, or its member companies, may be able to be more helpful on this issue. Based on our current knowledge regarding the data on the drug's safety and effectiveness, we estimate that the review process at the FDA would take approximately four to six months, which would include the involvement of a public advisory committee.

In response to your last question, an unresolved issue would be obtaining access in this country to a prostaglandin which, as you know, under the terms of the foreign approvals, must be taken in conjunction with mifepristone. In addition, as you are aware, distribution of mifepristone is closely controlled under the terms of the foreign approvals. The appropriate distribution system for mifepristone in this country would also need to be resolved.

Sincerely yours,

Carol R. Scheman

Carol R. Scheman
Deputy Commissioner
for External Affairs

102d Congress

United States House of Representatives
Committee on Small Business

Subcommittee on Regulation, Business Opportunities, and Energy

B-363 Rayburn House Office Building
Washington, DC 20515-6318

December 10, 1992

Dr. David A. Kessler
Commissioner
U.S. Food and Drug Administration
Room 14-71
5600 Fishers Lane
Rockville, Maryland 20857

Via Fax: (301) 443-3100

Dear Dr. Kessler,

This subcommittee is investigating several issues relating to the U.S. regulation of, and marketplace opportunities for the French drug RU 486, manufactured by Roussel Uclaf. Key to this inquiry is the current view of the U.S. Food and Drug Administration regarding the safety and efficacy proofs which will be required should the manufacturer decide to market this drug in the United States, and the time burden likely to face the company should it seek a new drug approval from your agency.

While the agency should not -- and does not -- intend to in any way lessen the normal burden of proof required for any new drug, in the case (prospectively) of RU 486, we are interested in whether scientists within the FDA's new drug approval section have any views regarding the breadth and quality of experience with this drug in France, and in other foreign markets.

In this context, I have several questions for the agency:

-- To what extent does the agency deem European experience with this drug, including more than 100,000 clinical medical cases in France since 1988, as evidence of the drug's safety and efficacy for purposes of approval in the United States?

-- If European experience with RU 486 is directly applicable to requirements demanded within the FDA standard drug approval process, is it possible to attach some comparative value to that which is already known about the drug?

Specifically, can you give a rough estimate as to the percentage or portion of the usual U.S. drug approval process, including demands for extensive human testing, which may already be satisfied by the European experience?

-- Similarly, can you provide any estimate as to how long a U.S. drug approval process would take in light of the extensive evidence of safety and effectiveness already available for RU 486? Perhaps the agency can point to the case of another foreign drug used extensively, and safely, overseas prior to the manufacturer's application for a U.S. drug approval?

-- Subcommittee staff have spoken with a number of U.S. pharmaceutical companies which have an interest in licensing and distributing RU 486, or a similar drug, in the U.S. These companies have suggested that U.S. approval of this drug, for the reasons mentioned above, would be relatively swift and inexpensive.

The representative of one firm interviewed by subcommittee staff estimated that the total cost would be well under $5 million -- a marked difference from the average cost of a full-scale, full-phase, drug approval process estimated by Tufts University at more than $200 million.

While this estimate of the possible cost of taking RU 486 through the U.S. drug approval process obviously is very speculative, would you say that this forecast still could be in the ballpark given what we know of the European experience with RU 486 in terms of safety and effectiveness, and whatever additional proofs may be demanded by the agency?

-- Finally, are you aware of any unusual or unique circumstances involving this drug which could delay, jeopardize or otherwise seriously impede its review in the FDA's drug approval process, should the company come forward with an application?

Thank you for your attention to these questions. I would very much appreciate your earliest possible response. Should you have any questions, please don't hesitate to contact me, or Steve Jenning of the subcommittee staff at (202) 225-7797.

Sincerely,

RON WYDEN
Chairman

cc. Congressional Affairs, FDA.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 14, 1992

Edouard Sakiz, M.D.
President, Roussel-Uclaf
102 Route de Noisy
F-93230 Romainville
France

Dear Dr. Sakiz:

In a December 7, 1992, article by William Drozdiak, a Paris reporter for the Washington Post, concerning the likelihood of RU-486 becoming available in this country for interruption of pregnancy, you are quoted as saying that "we [Roussel-Uclaf] are preparing to see how we can have a clinical trial start in the U.S." The same article also quotes me as saying that the Food and Drug Administration "would welcome an application" for your company's product.

There may be a misunderstanding regarding Federal Food, Drug, and Cosmetic Act requirements for drug approval. We accept foreign clinical trials, so long as we are able to audit the data, according to our normal procedures. Agency staff who will be responsible for reviewing the application report that based on publicly available information and literature, the available data may well be sufficient to permit an adequate review. In light of existing data, further clinical trials may not be required.

My colleagues and I would be pleased to discuss this issue with you further if that would be of help.

Sincerely yours,

David A. Kessler, M.D.
Commissioner of Food and Drugs

APPEARS THIS WAY
ON ORIGINAL

101st Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Building
Washington, DC 20515

May 24, 1990

James A. Benson
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Mr. Benson:

The Subcommittee is reviewing FDA's issuance of the June 9, 1989, automatic detention import alert on RU 486. I am concerned that the FDA has taken the position that this alert is justifiable on the grounds of health and safety risks. After reviewing many FDA documents relating to this decision, I cannot find specific documentation in FDA records attesting to the health and safety risks of RU 486.

In fact, the FDA has issued inconsistent, contradictory statements with respect to RU 486. For example, the agency states in its July 20, 1988 Pilot Guidance for Release of Mail Importations that any unapproved drug -- including RU 486 -- may be released to a patient, if the patient affirms in writing that it is for their "own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product."

Yet, June 9, 1989, the Agency appears to take a different position on RU 486. In a letter to Rep. Robert Dornan, Dr. Frank Young simply assumes that patients will use RU 486 without physician supervision -- and cites this assumption as creating a health and safety problem which is grounds for barring its use.

The only criteria the the FDA has used in finding RU 486 unsafe, is that it would be used without physician supervision. It does not appear from a review of FDA's files that the Agency has any evidence indicating that RU 486 would, in fact, be used without such supervision.

The FDA is treating RU 486 differently than other unapproved drugs, without any evidence that this treatment is warranted. The FDA appears to have tossed aside its physician supervision requirement for unapproved drugs, so that it can block physician supervised personal use of RU 486.

Additionally, in a memo to you from your chief counsel,

[redacted] dated February 23, 1990, [redacted] indicates that "...because of the number of inquiries that the districts had received regarding its "legal status" in the United States, an import alert was required to clarify that the product was unapproved and, as such, was prohibited." Additional documents on file buttress this point. The handwritten cover page of the clearance record on the import alert, written by [redacted] reads:

"Do [sic] to numerous inquiries to OLA/HFC-1/IOB and districts on suitability for entry of abortifacient (RU 486) drugs under the Pilot Guidance for Release of Mail Importation for personal use, this import alert establishes the agency's position on this question. The alert establishes the agencies that this product is not to be released under the pilot guide and the product is not suitable for personal use without proper supervision by a physician."

However, in a letter from your Associate Commissioner for Legislative Affairs, Hugh Cannon, dated April 3, 1990, Mr. Cannon notes that "We have not been able to identify any correspondence or other documents from the field...regarding RU-486."

On the basis of my staff's review of FDA's policies on RU 486, I would like to ask the following questions:

1) What evidence has the FDA gathered that indicates that RU 486 will be used without physician supervision?

2) Why has the FDA not applied its physician supervision requirement to RU 486 when it might ensure that RU 486 would be used safely?

3) Why has the FDA issued an import alert based upon inquiries from the field that have not been made?

4) What is the evidence of health or scientific risk that the Agency specifically used to issue the import alert for RU 486?

I would appreciate a prompt, written response to the above questions by June 22, 1990.

Sincerely,

Ron Wyden

RON WYDEN
Chairman

APPEARS THIS WAY
ON ORIGINAL

RW/gab

HFD - 1
L.R. 2
5
6
500
HFC - 2
(Action)

ROUTING AND TRANSMITTAL SLIP Date 5/29/90

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1.		
2.		
3.		
4.		
5.		

Action	File	Note and Return
Approval	For Clearance	Per Conversation
As Requested	For Correction	Prepare Reply
Circulate	For Your Information	See Me
Comment	Investigate	Signature
Coordination	Justify	

REMARKS

6.

Wyden Document Request

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
	Phone No.

5041-102

*U.S.G.P.O.: 1983 -421-529/320

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

APPEARS THIS WAY
ON ORIGINAL

ROUTING AND TRANSMITTAL SLIP

Date: 6/15/89

TO: (Name, office symbol, room number, building, Agency/Post)	Initials	Date
1. [redacted]		
2. [redacted]		
3. HFD-510/ [redacted]		
4. [redacted]		
5.		

	Action		File		Note and Return
	Approval		For Clearance		Per Conversation
	As Requested		For Correction		Prepare Reply
	Circulate	XX	For Your Information		See Me
	Comment		Investigate		Signature
	Coordination		Justify		

REMARKS

On 9/26/88, a interim "Import Bulletin" on RU-486 was issued; it stated that the product could not be imported by mail for personal use under the provisions of the 7/20/88 "Pilot Guidance for Release of Mail Importations." On 6/6/89, this policy was formalized by issuance of an "Import Alert" stating that RU-486 would not be allowed entry under the mail importation program.

APPEARS THIS WAY
ON ORIGINAL

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: (Name, org. symbol, Agency/Post)	Room No.—Bldg.
/S/	Phone No.

5041-102 ☆U.S. GPO: 1987—181-246/40023 **OPTIONAL FORM 41 (Rev. 7-76)** Prescribed by GSA FPMR (41 CFR) 101-11.206

file
mifepristar

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

JUN 09 1989

Dear Mr. Dornan:

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

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

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

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

APPEARS THIS WAY
ON ORIGINAL

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

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

Sincerely yours,

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

DATE: JUNE 6, 1989

FROM: ——— DIVISION OF FIELD INVESTIGATIONS (HFC-130)

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

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

——— (HFC-101)
INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)
OFFICE OF REGULATORY GUIDANCE (HFF-310)

——— (HFC-160)
——— (HFC-210)
——— (GCF-1)
OFFICE OF COMPLIANCE (HFF-300)
——— (HFD-300)
——— (HFV-230)
——— (HFZ-300)
FIELD PROGRAMS BRANCH (HFF-26)
——— (HFC-42)
——— (HFB-100)
——— (HFC-6)

OFFICE OF ENFORCEMENT (HFC-200)
——— (HFC-230)
——— (HFF-25)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
——— (HFY-50)
——— (HPB-CANADA)
——— (HFC-41)
——— (HFD-301)
——— (HFC-6)

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

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

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drug that induces abortion)

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

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

PAC : 56008H

COUNTRY : All

...EARS THIS WAY
...ORIGINAL

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

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

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

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

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

/s/

ROBERT K. DORNAN
38TH DISTRICT, CALIFORNIA

INTELLIGENCE COMMITTEE

ARMED SERVICES COMMITTEE
SUBCOMMITTEES:
COMBAT READINESS
RESEARCH AND DEVELOPMENT

SELECT COMMITTEE ON
NARCOTICS ABUSE AND CONTROL

PERMANENT OBSERVER TO
GENEVA ARMS TALKS

Congress of the United States
House of Representatives

CHAIRMAN
HOUSE REPUBLICAN STUDY
COMMITTEE

CHAIRMAN
RSC TASK FORCE ON
FOREIGN AFFAIRS

EXECUTIVE COMMITTEE
HOUSE REPUBLICAN RESEARCH
COMMITTEE

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

May 5, 1989

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

Dear Dr. Young:

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

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

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

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

We look forward to your prompt reply.

Sincerely,

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

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

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

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

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

APPEARS THIS WAY
ON ORIGINAL

D 502

MAY 02 1989

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

Dear Senator Helms:

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

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

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

We do not believe that this policy can be appropriately applied to the importation of RU-486 because use of the product could present an unreasonable safety risk. That is, the intended use of this drug makes it likely it would be used without benefit of supervision of a physician and indiscriminate or unsupervised use could be hazardous to the patient's health. This is because the drug has potential side effects such as uterine bleeding, severe nausea, vomiting, and weakness, which might require prompt medical intervention. Copies of our July 28, 1988 guidance and an import bulletin on RU-486 dated September 26, 1988 are enclosed for your information. Please note that this bulletin prevents to the best of our ability RU-486 from entering the country for safety reasons.

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely yours,

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

Enclosure

JESSE HELMS
NORTH CAROLINA

United States Senate

WASHINGTON, DC 20510

February 23, 1989

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

Dear Dr. Young:

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

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

Kindest regards.

Sincerely,

Jesse Helms

JESSE HELMS:mjc

APPEARS THIS WAY
ON ORIGINAL

JUL 20 1988

NOTE: THIS GUIDANCE IS BEING ISSUED ON A PILOT BASIS AND IS SUBJECT TO CHANGE AND/OR CANCELLATION. IF THE PILOT PROVES SUCCESSFUL, WITH NO SIGNIFICANT PROBLEMS, CHAPTER 9-71 OF THE REGULATORY PROCEDURES MANUAL MAY BE APPROPRIATELY REVISED.

SUBJ: Pilot Guidance for Release of Mail Importations

Because of the desire to acquire articles for treatment of serious and life-threatening conditions like AIDS and cancer, individuals have been purchasing unapproved products from foreign sources. Some of these products are sold over-the-counter in the country of origin while others are available from clinics where the purchaser was treated. Such products are often shipped to the purchaser by mail.

Even though such products are subject to refusal, we may use our discretion to examine the background, risk, and purpose of these products before making a final decision. To assure that the districts are operating in a uniform manner, the following guidance is provided for dealing with personal use shipments.

1. Except as modified by these instructions, established guidance found in RPM-9-71, exhibits X9-71-1 and X9-71-2 should be followed.

2. A product entered for personal use, which meets the criteria in item 4 below, may proceed without sampling or detention.

3. Products that are not identified, or are not accompanied by documentation of intended use, should be detained. Other reasons for detention may include: size of the shipment (amount inconsistent with personal use), fraudulent promotion or misrepresentation, or an unreasonable health risk due to either toxicity or possible contamination. In such cases, the appropppriate center should be contacted for guidance concerning release of the product.

4. Following detention, shipments may be released to an individual if the following criteria can be satisfied and there is no safety risk or evidence of fraud:

   - o the product was purchased for personal use
   - o the product is not for commercial distribution and the amount of product is not excessive (i.e., 3 months supply of a drug)
   - o the intended use of the product is appropriately identified
   - o the patient seeking to import the product affirms in writing that it is for the patient's own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product

5. If the district should encounter a situation suggesting promotional and/or commercial activity that falls within our health fraud guideline, the district should recommend that an Import Alert be issued for the automatic detention of the product and identification of the promoter involved.

6. The model letter currently in Exhibit X9-71-2 should be revised according to the attached during this pilot.

7. The article may then be RELEASED WITH COMMENT upon receipt of the letter as follows:

> "The drug you have obtained for your personal use appears to be unapproved in the U.S. We understand you will use this limited quantity under medical supervision; however, future personal shipments may be refused entry if we learn, among other things, the drug presents an unreasonable risk or it has been commercially promoted to U.S. citizens."

The above guidance should be used as part of the current outstanding instructions for dealing with mail packages as found in Chapter 9-71 of the RPM.

Import Operations Branch
5600 Fishers Lane
Rockville, MD 20857
(301) 443-6553

APPEARS THIS WAY
ON ORIGINAL

MODEL LETTER FOR USE IN DRUG MAIL

EXHIBIT X9-71-2

(LETTERHEAD)

A mail shipment of a drug from a foreign country addressed to you is being detained at the post office. All products of this kind must meet the requirements of the Federal Food, Drug, and Cosmetic Act, which is designed to protect you from unsafe or misrepresented foods, drugs, cosmetics and devices. Examination indicates that the product does not comply with the law.

Please read the enclosed Notice of Detention and Hearing carefully, since it explains why the product is believed to be in violation. The Notice does not in any manner accuse you of violating any law...

If the drug is not approved for distribution in the U.S., it may be released for your personal use provided you furnish the following:

> A letter providing adequate documentation that the product is for the patient's own use and the name and address of the doctor licensed in the United States responsible for his or her treatment with the product.

Send your statement to this office, and we will promptly review your submission and consider release of the product.

If you have good reason to believe the product does comply with the law and wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice.

If you do not wish to claim this shipment, you may disregard the Notice and the shipment will be returned to sender without cost to you.

Sincerely yours,

Enclosure

APPEARS THIS WAY
ON ORIGINAL

WPMAIL -ECHO
MAIL IMPORT-ALERT 'IMPORT ALERT #66-41'

DATE: AUGUST 1, 1988

FROM: [redacted] DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT ALERT #66-41 "UNAPPROVED NEW DRUGS PROMOTED IN THE U.S."

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)

[redacted] (HFC-160)
[redacted] (HFC-210)
[redacted] (GCF-1)
[redacted] (HFF-310)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
[redacted] (HFY-50)
[redacted] (HPB-CANADA)
[redacted] (HFC-41)
[redacted] (HFD-301)

OFFICE OF ENFORCEMENT (HFC-200)
[redacted] (HFC-230)
[redacted] (HFF-25)
OFFICE OF COMPLIANCE (HFF-300)
[redacted] (HFD-300)
[redacted] (HFV-230)
[redacted] (HFZ-300)
[redacted] (HFF-26)
[redacted] (HFC-42)
[redacted] (HFB-100)

TYPE OF ALERT: AUTOMATIC DETENTION

PRODUCT : Unapproved new drugs 66-----

PROBLEM : Unapproved drugs promoted in the U.S. (see attachment)

PAC : 56008H

COUNTRY : ALL

MANUFACTURER/
SHIPPER : See Attachment

REFERENCE : EMS "Pilot Guidance for Release of Mail Importation" dated 7-20-88.

Compliance Policy Guide (CPG) 7150.10 gives extensive background on health fraud, and the indirect risks of relying

on unproven remedies. Health fraud has been defined by the agency as the promotion of unproven medical products.

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

RECOMMENDING OFFICE : Import Operations Branch (HFC-131)

REASON FOR ALERT : Media reports concerning the referenced pilot guidance for release of mail importation have inaccurately suggested that any unapproved drug may be imported through the mail for personal use. The pilot guidance that issued is much more restrictive than reported. The pilot guidance was intended to be applicable only to (1) persons who have received treatment in a foreign country and who, upon returning to the United States, have imported the drug for their personal use in an effort to continue the treatment started abroad; and (2) persons who have made their own arrangements for obtaining drugs from foreign sources, when the drug has not been promoted in the United States.

Whenever there is evidence of promotion of unapproved drugs to persons in the United States, the products should be detained. Evidence of promotion may consist of solicitations for mail orders, press releases, advertising materials, and other public announcements that are directed to persons residing in the U.S.

Paragraph 5 of the pilot guidance was intended to recommend import alerts when the promotion of an unapproved product falls within CPG 7150.10 on health fraud. Thus, the field may recommend import alerts when a product meets the criteria for either a direct health hazard or indirect health hazard.

INSTRUCTIONS : Automatically detain any unapproved drug listed in the attachment.

Detain any other drug that fails to meet the discretionary release criteria in the referenced pilot guidance. For products detained and not listed in the attachment forward documentation for headquarters review to HFC-131. Do not refuse entry of unlisted products until notified in writing they will be added to this alert.

SPECIAL NOTE : Continue to enforce, as appropriate, related import alerts restricting fraudulent, dangerous, and commercial drug importations, e.g. I.A. #66-28, Automatic Detention of Unapproved New Drugs Promoted by Dr. Hans A. Nieper of West

Germany.

We expect additional firms that commercialize unapproved drugs will be added to the attached list. Separate import alerts will issue if products are encountered that centers believe are either direct or indirect health hazards.

FOI : No purging is required of this alert.

/s/

APPEARS THIS WAY
ON ORIGINAL

WPMAIL -ECHO
MAIL IMPORT-ALERT 'IMPORT BULLETIN 66-B13'

DATE: SEPTEMBER 26, 1988

FROM: [redacted] DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT BULLETIN #66-B13 "RU486"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

[redacted] (HFC-101)
INTERGOVERNMENTAL AND INDUSTRY
AFFAIRS STAFF (HFC-50)
DIVISION OF FIELD SCIENCE (HFC-140)
DIVISION OF FEDERAL-STATE RELATIONS (HFC-150)
OFFICE OF LEGISLATIVE AFFAIRS (HFW-10)
DIVISION OF REGULATORY GUIDANCE (HFF-310)

[redacted] (HFC-160)
[redacted] (HFC-210)
[redacted] (GCF-1)
OFFICE OF COMPLIANCE (HFF-300)
[redacted] (HFD-300)
[redacted] (HFV-230)
[redacted] (HFZ-300)
FIELD PROGRAMS BRANCH (HFF-26)
[redacted] (HFC-42)
[redacted] (HFB-100)
[redacted] (HFC-205)

OFFICE OF ENFORCEMENT (HFC-200)
[redacted] (HFC-230)
[redacted] (HFF-25)
PRESS OFFICE (HFI-20)
PRESS OFFICE (HFI-21)
[redacted] (HFY-50)
[redacted] (HPB-CANADA)
[redacted] (HFC-41)
[redacted] (HFD-301)
[redacted] (HFC-205)

* * * * * * * * B U L L E T I N * * * * * * * *

"RU486" or "Mifepristone" manufactured by Roussel Uclaf Laboratories, Paris France has been approved in France and in China. The drug is used to induce abortion and can be used up to 49 days after a woman's last menstrual period.

This drug will not be allowed entry under the "Pilot Guidance for Release of Mail Importations" which issued on July 20, 1988, because it does not meet the criteria in the policy statement.

/s/
[redacted]

APPEARS THIS WAY
ON ORIGINAL

terminate the pregnancy. Attachment A hereto at 3 and clinical information attached thereto at 3; see also Patient Informed Request, Exhibit B-3 to Plaintiffs' motion for preliminary relief.

Further, serious cardiovascular complications have occurred in women, including one fatality, when RU486 is used with certain prostaglandins that are no longer used in controlled settings, Attachment A hereto at clinical information attached thereto at 2, but might be used inadvertently in a less well-supervised environment.

These potential complications can be monitored and treated in a controlled clinical trial, but not in the context of personal use. In issuing the import alert, the agency was concerned not only with the risks of RU486, but also with the fact that RU486 does not meet the criteria of the personal import policy. The relevant portion of the personal import policy contains two parts which describe the situations in which it may be appropriate for field personnel to consider releasing an unapproved drug for personal use. RPM Ch. 9-71-30(C).

The first part of the policy applies to unapproved drugs that are not intended for the treatment of a serious condition and are ~~not~~ known to represent a significant health risk. See RPM 9-71-30(C). This provision is intended for such drugs as cold medications that a person might buy abroad to treat a minor illness while traveling and bring back into the United States. Exh. H to Plaintiff's Complaint at 36. RU486 does not qualify

under this provision because it is used for a serious condition and because its use, as discussed above, represents a significant health risk.

The second part of the policy applies to unapproved drugs that are, among other considerations, intended for a serious condition for which effective treatment may not be available domestically either through commercial or clinical means,[11] and are "considered not to represent an unreasonable risk." RPM Ch. 9-71-30(C). RU486 does not fall within this provision because it is proposed for use in treating a condition for which an alternative treatment does exist and because it poses a safety risk. Id.; RU486 Hearings at 36. Other means of abortion are available in the United States, and RU486 is not necessary to make abortion available. See RU486 Hearings at 36.[12] Moreover,

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[11] Such clinical means might include a clinical investigation pursuant to an IND.

[12] Plaintiff cites United States v. Diapulse, 748 F.2d 56 (2d Cir. 1984) in support of her argument that the agency may not allow some parties to avoid enforcement of the FDCA's new drug provisions, while requiring others who are similarly situated to follow them. Pl. Mem. at 11. Plaintiff's reliance on Diapulse is misplaced. The court in Diapulse found only that in the case before it FDA could not deny approval to a company seeking to market a device where it had granted such approval to another company for a closely similar device for the same uses. 748 F.2d at 62. FDA permits the importation of RU486 for use as an abortifacient when it is being imported for a clinical investigation pursuant to an IND; it does not permit the personal importation of RU486 for use as an abortifacient. Plaintiff's reasoning would require FDA to treat all unapproved new drugs alike. This approach is inconsistent with the personal import policy, a policy which reflects the agency's judgment that it is an appropriate exercise of enforcement discretion not to prevent the importation of an unapproved drug that poses some safety risks to treat a serious condition for which adequate alternative

(continued...)

Memorandum
October 5, 2000
To: [redacted] HFD-205
From: [redacted]
[redacted] Office of Review Management HFD-002
Subject FOI on mifepristone

[redacted]

I have not been involved in mifepristone issues for about 5 years. I did not retain files on the issue after the new Division ,HFD-580, dealing with reproductive matters was created and split-off from Division-510

However, as part of my duties in my current position I participated in several pre-approval meetings on mifepristone.
I sent the attached memos to the following individuals:
[redacted] (to whom the memo was addressed-she was at the time substituting for [redacted]
[redacted]
And copies to the following individuals:
[redacted]
[redacted]
[redacted]
[redacted]

I received no replies from any of the above named people.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: September 28, 2000

FROM: _____ /S/ SEP 28 2000

SUBJECT: _____ Memo

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and ~~1.3~~% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

APPEARS THIS WAY
ON ORIGINAL

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains Exelgyn Laboratories Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from Exelgyn in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided Exelgyn's 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

APPEARS THIS WAY
ON ORIGINAL

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Davidson
Former Member of the
Advisory Committee for Reproductive Health Drugs

With this FAX, we want to notify you that today the Food and Drug Administration approved the new drug application for Mifeprex (mifepristone).

Because you participated in providing advice to the Agency on this product and because the approval of this product is very controversial we want to inform you in as timely a manner as possible of our action.

We have attached the FDA press release announcing the decision. As you will see, an Agency telephone number is available at which Agency personnel can be reached to answer telephone calls from the public regarding the Agency's action on the product. That telephone number is: **1-888-463-6332.** Alternatively, you may call our office (**301-827-7001**) if you have questions and we will forward them on to the appropriate person within the Agency.

As also indicated in the press release, we have created a web site which we believe will answer most questions regarding the product. The web site can be found at: **http://www.fda.gov/cder/drug/infopage/mifepristone**

Attachment

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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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APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Jodi Lerner

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. LERNER.

THANK-YOU

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CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. James Trussell

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted](Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

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COMMENTS:

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THANK-YOU

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Trussell
Member of the Advisory Committee for Reproductive Health Drugs

With this FAX, we want to notify you that today the Food and Drug Administration approved the new drug application (NDA) for Mifeprex (mifepristone).

Because you participate as a member of the Advisory Committee which provided advice to the Agency on this product and because the approval of this product is very controversial we want to inform you in as timely a manner as possible of our action.

We have attached the FDA press release announcing the decision. As you will see, an Agency telephone number is available at which Agency personnel can be reached to answer telephone calls from the public regarding the Agency's action on the product. That telephone number is: **1-888-463-6332**. Alternatively, you may call our office (**301-827-7001**) if you have questions and we will forward them on to the appropriate person within the Agency.

As also indicated in the press release, we have created a web site which we believe will answer most questions regarding the product. The web site can be found at: **http://www.fda.gov/cder/drug/infopage/mifepristone**

Attachment

APPEARS THIS WAY
ON ORIGINAL

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

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- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
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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/

####

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Richard Falk

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. FALK.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Richard Falk
Member of the Advisory Committee for Reproductive Health Drugs

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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.

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APPEARS THIS WAY
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Michael Greene

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. GREENE.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Greene
Member of the Advisory Committee for Reproductive Health Drugs

With this FAX, we want to notify you that today the Food and Drug Administration approved the new drug application (NDA) for Mifeprex (mifepristone).

Because you participate as a member of the Advisory Committee which provided advice to the Agency on this product and because the approval of this product is very controversial we want to inform you in as timely a manner as possible of our action.

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

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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

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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
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- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
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####

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Bonnie Dattel

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. DATTEL.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Dottel
Member of the Advisory Committee for Reproductive Health Drugs

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September 28, 2000
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FOOD AND DRUG ADMINISTRATION
Print Media: 301-827-6250
Broadcast Media: 301-827-3434
Consumer Inquiries: 888-INFO-FDA

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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

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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.

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- Current long-term therapy with corticosteroids
- History of allergy to mifepristone, misoprostol or other prostaglandins
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APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Dr. Joseph Harris

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: **6** (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. HARRIS.

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Dr. Harris
Member of the Advisory Committee for Reproductive Health Drugs

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ADVISORS AND CONSULTANTS STAFF
5630 Fishers Lane, Room 1093
Rockville, Maryland 20857
TELE: [redacted]
FAX: [redacted]

facsimile
TRANSMITTAL

TO: Ms. Deborah L. Narrigan, M.S.N., C.N.M.

FROM: [redacted]
FDA, Advisors and Consultants Staff
[redacted] (Direct line)

FAX #: [redacted]

TELEPHONE #: [redacted]

RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO Ms. NARRIGAN

THANK-YOU

APPEARS THIS WAY
ON ORIGINAL

[redacted]

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 28, 2000

From: Advisors and Consultants Staff
CDER/FDA

Subject: FDA Approval of MIFEPREX (mifepristone)

To: Ms Dr. Harrigan
Former Member of the
Advisory Committee for Reproductive Health Drugs

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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

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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

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- 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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RE: ****PLEASE SEE ATTACHED MEMO**

DATE: September 28, 2000

PAGES: 6 (including cover sheet)

COMMENTS:

PLEASE IMMEDIATELY FORWARD THIS FAX TO DR. LEWIS.

THANK-YOU

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