'ILLIAM F. CLINGER, JR.
5TH DIS'RICT, PENNSYLVANIA

WASHINGTON OFFICE
2160 RAYBURN BUILDING
(202) 225-5121

DISTRICT OFFICES
SUITE 116
315 S. ALLEN STREET
STATE COLLEGE, PA 16801
(814) 238-1776

605 INTEGRA BANK BUILDING
WARREN, PA 16365
(814) 726-3910

Congress of the United States
House of Representatives
Washington, DC 20515-3805

COMMITTEE
GOVERNMENT OPERATIONS
RANKING REPUBLICAN MEMBER
PUBLIC WORKS AND
TRANSPORTATION

SUBCOMMITTEE ON AVIATION
RANKING REPUBLICAN MEMBER
SUBCOMMITTEE ON WATER RESOURCES
SUBCOMMITTEE ON SURFACE TRANSPORTATION

ASSISTANT REGIONAL WHIP

July 4, 1994

Mr. Gerald Mande
Legislative Affairs
Food and Drug Administration
Parklawn Building, 5600 Fishers Ln.
HFW-1, Room 15-55
Rockville, Maryland 20857

Dear Mr. Mande:

I am writing on behalf of my constituent, _____

_____ is very concerned about the drug RU-486. I would greatly appreciate your assistance in responding to _____ concerns, outlined in her attached letter.

Thank you for your time and prompt consideration. Please forward any correspondence to my Washington, D.C. office.

Sincerely,

Bill Clinger

Bill Clinger
Member of Congress

WFC:ajb

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 19 1994

The Honorable John Breaux
United States Senate
Washington, D.C. 20510-1803

Dear Senator Breaux:

This is in response to your letter of June 9, 1994, on behalf of _____ concerning RU-486, an abortifacient approved in France.

RU-486 has not received approval from the Food and Drug Administration (FDA) for marketing, although this drug is in clinical trials for treatment of a few conditions.

FDA reviews drugs but does not test them. Drug sponsors, generally manufacturers, arrange for testing by experts, as well as shouldering the cost, and include the results in new drug applications (NDAs).

Before FDA will permit testing of a drug in humans, the sponsor of the drug must provide us with information demonstrating that the drug is reasonably safe to administer to humans. The sponsor must also provide manufacturing and control data, a detailed protocol of study, and names and qualifications of investigators who will be performing the clinical trials.

The Federal Food, Drug, and Cosmetic Act, which we administer, sets forth the criteria for approval of new drugs. Approval is based on submission of data collected during the course of an investigation which demonstrates the drug is safe and effective for the purpose of use. Our review is based on an impartial evaluation of the scientific data.

Ethical concerns similar to your constituent's have been expressed by others. We appreciate these concerns and respect their personal opinion. We hope, however, that you will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such action are submitted to the agency.

It is too early to comment whether this drug will be safe and effective for any conditions under study. For your information, we have enclosed a formal statement presented by Commissioner David Kessler at a May 16, 1994, Congressional hearing.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFA-12	/S/	7/19						

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

MIF 006102

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely yours,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10(2)
ES/PHS(2) T70220
CCU 0621940003

R/D: [redacted] 7/14/94:(based on CDER draft)
R/T: [redacted] 7/14/94
F/T: [redacted] 7/14/94
No. 94 6316
(s:\wp\[redacted]\[redacted] ru-486)

APPEARS THIS WAY
ON ORIGINAL

JOHN BREAUX
LOUISIANA

MAJORITY
CHIEF DEPUTY WHIP

COMMITTEES

COMMERCE, SCIENCE, AND TRANSPORTATION

FINANCE

SPECIAL COMMITTEE ON AGING

WASHINGTON OFFICE
(202) 224-4623

United States Senate

WASHINGTON, DC 20510

STATE OFFICES

ONE AMERICAN PLACE, SUITE 2030
BATON ROUGE, LA 70825
(504) 382-2050

THE FEDERAL BUILDING
705 JEFFERSON STREET, ROOM 103
LAFAYETTE, LA 70501
(318) 262-6871

WASHINGTON SQUARE ANNEX BUILDING
211 NORTH 3RD STREET, ROOM 102A
MONROE, LA 71201
(318) 325-3320

HALE BOGGS FEDERAL BUILDING
501 MAGAZINE STREET, SUITE 1005
NEW ORLEANS, LA 70130
(504) 589-2531

CENTRAL LOUISIANA
(318) 487-8445

June 9, 1994

Mr. Gerry D. Klepner
Assistant Secretary for Legislation
U.S. Department of Health & Human Services
HHH Bldg, Room 416 G
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mr. Klepner:

I have been contacted by [redacted] of [redacted] regarding his concern over the introduction of RU-486 into this country.

Please investigate the enclosed information sent to me and provide me with a report giving the current status of RU-486. Your reply may be forwarded to the attention of Denise Gremillion Riemer in my Washington, D.C. office.

Thank you for your attention and assistance.

Sincerely,

John

JOHN BREAUX
United States Senator

JB:dgr/mgr
Enclosure

TRACER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FILE Rousset-UCAP

SEP 18 1995

The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

It has come to our attention that as a co-signator of the Citizen Petition regarding the Food and Drug Administration's (FDA) review of a new drug application for RU-486, you may not have received a response regarding the petition. The Agency did not respond to each of the petitioners individually. A formal response, however, was sent on March 20, 1995 to Mr. Gary Yingling, McKenna & Cuneo, who had filed the petition on behalf of the petitioners. For your information, we are enclosing a copy of that letter.

If you have any further questions about this matter, please contact ——— of my staff at ———.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc: HFW-10(2)
HFW-14(Plaisier)
R/D: ———:9/1/95
Edit: ———:9/4/95
R/T:lmb:9/6/95 CHAIRMAN\RU-486.PET)
Edit: ——— 9/6/95
F/T: —:9/16/95
95-8534

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FILE	HFW12	/S/	9/18/95						
COPY									

MIF 006105

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 20, 1995

Mr. Gary L. Yingling
McKenna & Cuneo
1575 Eye Street, N.W.
Washington, D.C. 20005

Dear Mr. Yingling:

We have received the petition you filed on February 28, 1995, regarding our review of a new drug application for mifepristone as an abortifacient. The petition has stated many concerns and considerations related to the safe and effective use of mifepristone as an abortifacient.

The Food and Drug Administration is prohibited from publicly disclosing the existence of an application unless its existence has been previously publicly disclosed or acknowledged (21 C.F.R. § 314.430(b)). However, if, and when, such an application is submitted to the Agency, please be assured that we will review it in accordance with the statutory criteria set forth in the Federal Food, Drug, and Cosmetic Act. As you know, such a review requires the Agency to review both the safety and effectiveness of the drug, among other factors.

Your petition has been provided to the Center for Drug Evaluation and Research for its information and consideration in its review of any application that may be submitted.

Please consider this in full response to your petition, docket number 95P-0054/CP 1.

Sincerely yours,

Ronald G. Chesemore
for Associate Commissioner for
Regulatory Affairs

FILE

Memorandum

August 21, 1995

NOTE TO:

Through: , PHS ____

FROM: Director
FDA Executive Secretariat

SUBJECT: Fact Sheet on RU-486 (Tracer 22700)

Attached is FDA's fact sheet on RU-486 for the Secretary's briefing book on the upcoming Fourth World Conference on Women.

Please feel free to call me if you have any questions.

151

Attachment

APPEARS THIS WAY
ON ORIGINAL

151 11/9/95

RU-486

RU-486 (mifepristone) is manufactured by the French firm Roussel-Uclaf, a subsidiary of Hoechst AG, and the drug is approved as an abortifacient in France, the United Kingdom, and Sweden. Although the drug has not been approved for marketing in the U.S., there are several investigational new drug (IND) applications on file with FDA for various uses--abortifacient, contraception, Cushing's Syndrome, diabetes, meningioma, and breast cancer. Specific information about these INDs is considered confidential information. Hoechst AG had historically refused to permit Roussel-Uclaf to seek marketing approval as an abortifacient for RU-486 in the U.S.

In June 1989, after questions had been raised concerning whether RU-486 should be imported under FDA's personal use importation policy, the Agency issued an import alert on RU-486. FDA stated that the drug would be inappropriate for release under the policy and that the intended use could pose a risk to the safety of the user. The import alert was challenged on July 1, 1992, when FDA and the Custom Service detained a small quantity of RU-486 from a woman entering the U.S. at Kennedy Airport in New York. That case is still being litigated.

On January 22, 1993, President Clinton issued a memorandum directing Secretary Shalala to promote the testing, licensing, and manufacturing in the U.S. of RU-486 and to direct FDA to reassess whether RU-486 qualifies for FDA's personal use importation exemption. FDA continues to maintain that the import alert is necessary because of safety concerns.

After much negotiation between HHS officials, the Population Council, and representatives of Hoechst AG and Roussel-Uclaf, on May 16, 1994, the Population Council and Roussel-Uclaf announced that Roussel-Uclaf would turn over to the Population Council the U.S. rights for all identified medical uses of mifepristone. The Population Council plans to locate a manufacturer and announced on October 27, 1994, that it had begun clinical trials of mifepristone as an abortifacient in the U.S. The trials are ongoing.

Subject Areas for Fact Sheets on Women's Health

Public Health Service

Access to Health Care – HRSA
Breast Cancer – OWH to Coordinate w/ appropriate agencies
Family Planning – OPA
HIV/AIDS – OHIV/AP
Infant Mortality and Prenatal Care Initiatives – HRSA
International Conference on Population and Development – OIRH to Coord. w/a
Mental Health – NIH to Coordinate w/ appropriate agencies
NIH Women's Health Initiative – NIH
Preventive Care – CDC
RU-486 – FDA to Coordinate w/ NIH
Sexually Transmitted Diseases – CDC
Substance Abuse – SAMHSA
Tobacco – CDC
Women's Health and the Environment – CDC

Health Care Financing Administration

Hyde Amendment
Medicare Initiatives
Medicaid Initiatives

Administration for Children and Families

Child Care
Child Support Enforcement
Family Preservation and Support
Violence--Domestic, Family and Violence Against Women (coordinate with PHS)

Administration on Aging

Initiative on Older Women

Assistant Secretary for Health Planning and Evaluation

Health Care Reform
Welfare Reform

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FILE

AUG 11 1995

The Honorable Charles S. Robb
United States Senator
Old City Hall
1001 East Broad Street
Richmond, Virginia 23219

Dear Senator Robb:

This is in response to your letter of July 10, 1995, on behalf of [redacted] regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception, Cushing's syndrome, endometriosis, meningioma and breast cancer.

It is also important to point out that FDA does not actually do the clinical testing of drugs before they are marketed. Pharmaceutical manufacturers, the National Institutes of Health,

	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
FILE	HFA12	/S/	8/7/95						
COPY									

MIF 006110

and other research institutions across the country carry out programs to identify, develop and test drugs. It is FDA's responsibility to review and analyze the results of the testing to determine if a drug is safe and effective for widespread marketing for use by the general public.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10(2)
HFW-14
F/D: 7/22/95
F/T:lmb:8/3/95 \RU-486.rob)
Control No. 95-6610

APPEARS THIS WAY
ON ORIGINAL

CHARLES S. ROBB
VIRGINIA

STATE OFFICE:
Old City Hall
1001 East Broad Street
Richmond, VA 23219
(804) 771-2221

United States Senate

WASHINGTON, DC 20510-4603

COMMITTEES:
ARMED SERVICES
FOREIGN RELATIONS
INTELLIGENCE
JOINT ECONOMIC COMMITTEE
Vice Chairman
Democratic Policy Committee

July 10, 1995

Ms. Diane E. Thompson
Food and Drug Administration
Assoc. Commissioner for Leg. Affairs
1555 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Thompson:

Enclosed is correspondence I received in reference to a matter involving your agency. Your assistance with the requests and concerns expressed in this case would be greatly appreciated.

It would be very helpful if you would reply in duplicate and return the enclosure. In your reply, please reference

Your correspondence should be mailed to my office at the address indicated above.

Again, thank you for your assistance.

Sincerely,

Charles S. Robb

CSR\jbp
Enclosure

APPEARS THIS WAY
ON ORIGINAL

No. 95-6610

Washington Office:
Russell Senate Office Building
First and Constitution Avenue, NE
Room 154
Washington, DC 20510
(202) 224-4024

Regional Offices:
Dominion Towers, Suite 107
999 Waterside Drive
Norfolk, VA 23510
(804) 441-3124

8229 Boone Boulevard
Suite 888
Vienna, VA 22182
(703) 356-2006

Dominion Bank Building
Main Street
Clintwood, VA 24228
(703) 926-4104

Signet Bank Building
530 Main Street
Danville, VA 24541
(804) 791-0330

Crestar Bank Building
310 First Street SW, Suite 102
Roanoke, VA 24011
(703) 985-0103

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 19 1995

The Honorable Wendell H. Ford
United States Senate
Washington, D.C. 20510-1701

Dear Senator Ford:

This is in response to your letter of May 22, 1995, on behalf of, [redacted] regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

The petition to which your constituents refers has been provided to the Center for Drug Evaluation and Research for its information and consideration in its review of any application that may be submitted.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception,

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFA12	TST	9/15/95						

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

MIF 006113

Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituents' personal opinion on this issue. However, we hope that [redacted] will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure
Constituent's letter

cc: HFW-10 (2)
HFW-14 [redacted]

R/D: [redacted] 07/05/95
Edit: [redacted] :07/06/95
F/T:aor:07/14/95
s:\wp\ [redacted] \ru-pet.whf
FDA Control No. 95 4832

APPEARS THIS WAY
ON ORIGINAL

May 15, 1995

The Honorable Wendell H. Ford
U.S. Senate

Dear Sir:

We are writing in regards to the 100 page petiton (docket number 95P-0054/CP1), concerning the drug RU-486. We are aware that it was signed by 23 members of Congress and seven medical experts, and alerts the FDA and potential drug manufacturers to the health risks associated with this drug. We urge you to sign on to the petition opposing FDA approval of RU-486 & to call for hearings on the abortion drug based on sound reasons of medical science rather than for political or ideological reasons.

Sincerely,

[ ]

WENDELL H. FORD
KENTUCKY

COMMITTEES:
COMMERCE, SCIENCE, AND TRANSPORTATION
ENERGY AND NATURAL RESOURCES
RULES AND ADMINISTRATION

United States Senate

WASHINGTON, DC 20510–1701

May 22, 1995

TO: Diane E. Thompson
Associate Commissioner for Legislative Affairs
Food and Drug Administration
U.S. Department of Health and Human Services
1555 Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

RE: Enclosed

This office desires to be quickly and thoroughly responsive to all inquiries and communications. Your consideration and report regarding the enclosed is respectfully requested in duplicate along with the return of the enclosed. I appreciate your attention to this matter.

Please address envelope only to the attention of:

Christine Blakeslee
Office of Senator Wendell Ford
173A Russell Senate Office Building
Washington, DC 20510

Sincerely,

Wendell Ford

APPEARS THIS WAY
ON ORIGINAL

95-4832

DISTRICT OFFICES:
☐ 343 WALLER AVENUE
LEXINGTON, KY 40504
(606) 233-2484

☐ 1072 NEW FEDERAL BUILDING
LOUISVILLE, KY 40202
(502) 582-6251

☐ 19 U.S. POST OFFICE AND COURTHOUSE
COVINGTON, KY 41011
(606) 491-7929

☐ 305 FEDERAL BUILDING
OWENSBORO, KY 42301
(502) 685-5158

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 19 1995

The Honorable Pete V. Domenici
United States Senate
Washington, D.C. 20510-3101

Dear Senator Domenici:

This is in response to your letter of June 23, 1995, on behalf of _____ regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

The petition to which your constituent refers has been provided to the Center for Drug Evaluation and Research for its information and consideration in its review of any application that may be submitted.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception,

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFA-2	TSI	7/5/95						

MIF 006117

Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituent's personal opinion on this issue. However, we hope that [redacted] will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10 (2)
HFW-14 [redacted]

R/D: [redacted]:07/05/95
Edit: [redacted] :07/06/95
F/T: [redacted] :07/14/95
s:\wp\ [redacted] ,ru-pet.pvd
FDA Control No. 95 5963

APPEARS THIS WAY
ON ORIGINAL

PETE V. DOMENICI
NEW MEXICO

COMMITTEES:
BUDGET
APPROPRIATIONS
ENERGY AND NATURAL RESOURCES
INDIAN AFFAIRS

United States Senate

WASHINGTON, DC 20510-3101

June 23, 1995

Dianne Thompson
Legislative Affairs
Food & Drug Administration
5600 Fishers Lane
Room 1555
Rockville, Maryland 20857

Dear Dianne:

Because of my desire to be responsive to all inquiries directed to me, and knowing that you share this desire, the attached letter is referred to you for consideration.

I would very much appreciate your evaluating the information presented and taking whatever action is required to resolve the situation. I appreciate your consideration of this request, recognizing that it will be taken within the context of your existing procedures.

At your earliest convenience, I would be grateful for your findings and views, in duplicate form. Please send your response to the attention of James Fuller.

Sincerely,

Pete V. Domenici
United States Senator

PVD:jef
Enclosure

APPEARS THIS WAY
ON ORIGINAL

No. 95-5963

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 18 1995

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

Dear Senator Nunn:

This is in response to your letter of June 1, 1995, on behalf of [redacted] regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

The petition to which your constituent refers has been provided to the Center for Drug Evaluation and Research for its information and consideration in its review of any application that may be submitted.

5944

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OLA	/S/	7/14/95						
HFM-2	/S/	7/18/95						

*U.S. GPO: 1988-216-466

MIF 006120

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception, Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituent's personal opinion on this issue. However, we hope that [redacted] will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10 (2)
HFW-14

R/D: [redacted] 07/05/95
Edit: [redacted] :07/06/95
F/T:aor:07/14/95
s:\wp\ [redacted] \ru-pet.sn
FDA Control No. 95 5756

APPEARS THIS WAY
ON ORIGINAL

United States Senate
COMMITTEE ON ARMED SERVICES
WASHINGTON, DC 20510-6050

June 1, 1995

David A. Kessler
Food and Drug Administration
Commissioner
5600 Fisher's Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

I recently received the enclosed inquiry from one of my constituents. Please review the matter thoroughly, in accordance with established policies and procedures, and provide me with a full report.

I look forward to hearing from you in the very near future.

Sincerely,

Sam Nunn

SN:pmm

Enclosure

PLEASE REPLY TO:
Office of Senator Sam Nunn
Attn: Patricia Murphy
75 Spring Street
Suite 1700
Atlanta, Georgia 30303
404/331-4811

APPEARS THIS WAY
ON ORIGINAL

No. 95-5756

MIF 006122

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 18 1995

The Honorable Paul Simon
United States Senate
230 South Dearborn
Kluczynski Building, 38th Floor
Chicago, Illinois 60604

Dear Senator Simon:

This is in response to your letter of June 8, 1995, on behalf of _____ concerning compassionate use of the drug RU-486 for the treatment of a brain tumor. We are sorry to hear of her diagnosis.

As you know, the Food and Drug Administration (FDA) regulates the manufacture, sale, and distribution of drugs in the United States under the authority of the Federal Food, Drug, and Cosmetic (FDC) Act. That law defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed in interstate commerce (except for clinical study) until a sponsor, usually the drug's manufacturer, has submitted, and FDA has approved, a New Drug Application (NDA) for it. For approval, the NDA must contain substantial scientific evidence of safety and effectiveness for the drug's use as labeled. FDA has authority under the FDC Act to approve drugs only after they have been shown to be safe and effective.

In order to study the safety and effectiveness of a new drug, the sponsor (a pharmaceutical company, private, academic or other organization, or an individual) is required to file an Investigational New Drug (IND) application with FDA. Once accepted, the IND allows the sponsor to ship the drug in interstate commerce for research purposes only. The responsibility for the clinical trials and distribution of the drug falls upon the holder of the IND.

When the sponsor determines that adequate and well-controlled studies showing the drug is safe and effective have been carried out, that information, coupled with information on the manufacturing procedures and controls used in producing the drug, is submitted to FDA in the form of an NDA. After comprehensive review by FDA, the NDA is either approved or not approved; upon approval the drug may be marketed.

	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
FILE	OCA	/S/	7/5/95						
COPY	HFW-2	/S/	7/6/95						

MIF 006123

Patient access to drugs in investigational status is a complex issue. When a disease is severe and lacks effective therapy, there is tremendous desire and pressure to use the drug primarily as a treatment before it is approved. For many years, FDA has allowed such use under certain circumstances and, in 1987, FDA published regulations that formally recognized the treatment IND and clarified the conditions under which a treatment IND is appropriate. Where the available data are not sufficient to support a treatment IND such as when controlled clinical trials have not been completed, sponsors may conduct an open-label safety protocol where all patients receive active drugs and the safety of the drug is studied.

A physician may wish to explore the use of an individual investigator IND with the sponsor. However, this process is dependent upon the sponsor supplying the drug for this purpose. We can, and do, encourage sponsors to provide access to promising agents when there is potential benefit to patients, but, as a regulatory agency, we do not have the authority to require that a sponsor do so.

If your constituent's physician believes RU-486 may be of value in treating [redacted], the physician should contact a medical officer in FDA's Division of Oncology and Pulmonary Drug Products at [redacted] for further information.

We hope this information is helpful. If we can be of further service, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10 (2)
HFW-14 [redacted]
R/D:) [redacted] :7/3/95 [redacted] ru2)
Review: [redacted] 7/3/95
Control 95-5752

APPEARS THIS WAY
ON ORIGINAL

PAUL SIMON
ILLINOIS

COMMITTEES
LABOR AND HUMAN RESOURCES
JUDICIARY
FOREIGN RELATIONS
BUDGET
INDIAN AFFAIRS

United States Senate

WASHINGTON, DC 20510-1302

June 8, 1995

Mr. Hugh C. Cannon
Food and Drug Administration
Associate Commissioner for Legislative Affairs
U.S. Department of Health and Human Services
5600 Fishers Lane; 1555 Parklawn Building
Rockville, Maryland 20857

Dear Mr. Cannon:

I received the enclosed correspondence from my constituent, _____ concerning compassionate use of the drug RU486 for treatment of a brain tumor. For a more detailed explanation, please see the attached information.

I would appreciate your looking into this matter and advising Ms. Monica Brown, staff assistant in my Chicago office, of your findings as soon as possible.

Thank you for your cooperation and assistance.

Cordially,

Paul Simon
U. S. Senator

230 South Dearborn (3892)
Chicago, Illinois 60604
(312) 353-4952

PS/mjb
Enclosure

APPEARS THIS WAY
ON ORIGINAL

95-5752

462 DIRKSEN BUILDING
WASHINGTON, DC 20510-1302
202/224-2152
TDD: 202/224-5469

230 S. DEARBORN
KLUCZYNSKI BLDG., 38TH FLOOR
CHICAGO, IL 60604
312/353-4952
TDD: 312/786-0308

3 WEST OLD CAPITOL PLAZA
SUITE 1
SPRINGFIELD, IL 62701
217/492-4960
TDD: 217/544-7524

250 WEST CHERRY
ROOM 115-B
CARBONDALE, IL 62901
618/457-3653

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 19 1995

The Honorable Tom Harkin
United States Senate
Washington, D.C. 20510-1502

Dear Senator Harkin:

This is in response to your letter of May 10, 1995, on behalf of [redacted] regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

The petition to which your constituent refers has been provided to the Center for Drug Evaluation and Research for its information and consideration in its review of any application that ~~may be~~ submitted.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception,

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OLA	/S/	7-19-95						
HFD-78	/S/	7/15/95						

Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituent's personal opinion on this issue. However, we hope that [redacted] will understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure
Constituent's letter

cc: HFW-10 (2)
HFW-14 [redacted]

R/D: [redacted] :07/05/95
Edit: [redacted] :07/06/95
F/T: [redacted] :07/14/95
s:\wp\ [redacted] \ru-pet.th
FDA Control No. 95 4618

APPEARS THIS WAY
ON ORIGINAL

72135

Senator Tom Harkin
531 Hart Senate Office Building
Washington, D.C. 20515

Dear Senator Harkin,

Currently there is a petition before the FDA requesting that the fast track status of RU486 be revoked. This has been initiated by approximately 23 legislators in Washington D.C. urging the food and drug administration to more closely investigate FU486 and subsequently take the abortion inducing drug off of it's current fast track approval status.

This letter is to urge you to please sign and endorse the petition that has been sent to the FDA by these legislators.

As a physician and surgeon, I feel that RU486 has not been appropriately investigated and there are many hidden dangers which I feel could lead to unnecessary suffering by the users of this medication. First of all the federal food, drug and cosmetic act requires that the FDA withhold approval of any drug that is potentially ineffective or harmful. The FDA is obligated to investigate studies that reveal increased genetic risk to minorities, as well as to obese women and women with aids, as well as those with other medical conditions. Additionally all of the medical risks of surgical abortions, such as uterine bleeding and infection do indeed exist with RU486. In addition to side effects of the RU486 prostoglanin combination. Many reports out of Europe reveal that many women have been subjected to these problems and the subsequent consequences. Furthermore the long term studies of the effects RU486 on fertility, surviving children from the use of the medication and subsequent children have not been conducted.

I know that you are probably under emence pressure from the pro choice lobbiest to endorse and support this medication, but I personally feel that this medication has not been proven to be safe and effective and secondly, only adds to the plight of the millions of abortions that are performed in this country with the subsequent social and moral ramifications that occur with this problem.

Again I urge you to endorse the current petition before the FDA to take RU486 off of its fast track approval status.

Sincerely.

151

TOM HARKIN
IOWA

(202) 224-3254
TTY (202) 224-4633

COMMITTEES:
AGRICULTURE
APPROPRIATIONS
SMALL BUSINESS
LABOR AND HUMAN RESOURCES

United States Senate

WASHINGTON, DC 20510-1502

May 10, 1995

Dr. David Kessler
Commissioner
U.S. Food and Drug Administration
Office of Legislative Affairs
5600 Fisher's Lane, HFW10
Rockville, MD 20852

Dear Dr. Kessler:

Enclosed is a letter from one of my constituents who has a concern over the administration's policy on the testing and approval of RU-486. I respectfully ask you to review the administration's policy on this issue and send me a clarification so that I might be able to respond to my constituent's questions. It would be helpful if you could mark your correspondence with my office to the attention of Walter Harp.

Thank you in advance for your assistance on this matter.

Sincerely,

Tom Harkin
United States Senator

TH/wh

APPEARS THIS WAY
ON ORIGINAL

BOX 74884
CEDAR RAPIDS, IA 52407-4884
(319) 365-4504

210 WALNUT ST.
733 FEDERAL BLDG.
DES MOINES, IA 50309
(515) 284-4574

131 E. 4TH ST.
314B FEDERAL BLDG.
DAVENPORT, IA 52801
(319) 322-1338

350 WEST 6TH ST.
315 FEDERAL BLDG.
DUBUQUE, IA 52001
(319) 582-2130

320 6TH ST.
110 FEDERAL BLDG.
SIOUX CITY, IA 51101
(712) 252-1550

BARBARA BOXER
CALIFORNIA

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS

COMMITTEE ON BANKING, HOUSING, AND URBAN AFFAIRS

COMMITTEE ON THE BUDGET

JOINT ECONOMIC COMMITTEE

DEPUTY WHIP

United States Senate
HART SENATE OFFICE BUILDING
SUITE 112
WASHINGTON, DC 20510-0505
(202) 224-3553

1700 MONTGOMERY STREET
SUITE 240
SAN FRANCISCO, CA 94111
(415) 403-0100

2250 EAST IMPERIAL HIGHWAY
SUITE 545
EL SEGUNDO, CA 90245
(310) 414-5700

525 B STREET
SUITE 990
SAN DIEGO, CA 92101
(619) 239-3884

2300 TULARE STREET
SUITE 130
FRESNO, CA 93721
(209) 497-5109

June 9, 1995

Ms. Diane Thompson
Associate Commissioner for Legislative Affairs
Food and Drug Administration
5600 Fishers Lane
HFW-1, Room
Rockville, Maryland 20857

Dear Ms. Thompson:

I am writing on behalf of my constituent, [redacted] to convey her concerns about the approval process for the drug RU-486.

I have enclosed [redacted] correspondence for your consideration and review. I would appreciate it if you would respond to her directly.

Thank you in advance for your prompt attention to this matter.

Sincerely,

Barbara Boxer

Barbara Boxer
United States Senator

BB:EW
cc: [redacted]
Enclosure

APPEARS THIS WAY
ON ORIGINAL

No. 95-5211

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 10 1995

The Honorable Jon Kyl
United States Senate
Washington, D.C. 20510-0304

Dear Senator Kyl:

This is in response to your letters of May 12 and June 19, 1995, on behalf of [redacted] regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

As [redacted] mentioned, RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception, Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituent's personal opinion on this issue. However, we hope that [redacted] will

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OLA	/S/	7/7/95						
[illegible]	/S/	7/7/95						

understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10 (2)
HFW-14

R/D: :07/05/95
Edit :07/06/95
F/T: :07/07/95
s:\wp\ /ru-486.jk
FDA Control No. 95 4672

APPEARS THIS WAY
ON ORIGINAL

JON KYL
ARIZONA
702 HART SENATE OFFICE BUILDING
(202) 224-4521

COMMITTEES:
JUDICIARY
INTELLIGENCE
ENERGY AND NATURAL RESOURCES

United States Senate

WASHINGTON, DC 20510-0304

STATE OFFICES:
2200 EAST CAMELBACK ROAD
SUITE 120
PHOENIX, AZ 85016
(602) 840-1891

7315 NORTH ORACLE ROAD
SUITE 220
TUCSON, AZ 85704
(602) 575-8633

June 19, 1995

Congressional Liaison
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Congressional Liaison:

On May 12, I had written you about a constituent's concern regarding the abortifacient drug, RU-486. A copy of my letter is enclosed.

I am still concerned about the matter, and I would appreciate it if you could let me know when I could expect a reply. I will look forward to hearing from you in the near future.

Sincerely,

JON KYL
United States Senator

JK:tg

Enclosure

APPEARS THIS WAY
ON ORIGINAL

followup to
95-4672

MIF 006133

JON KYL
ARIZONA
702 HART SENATE OFFICE BUILDING
(202) 224-4521

COMMITTEES:
JUDICIARY
INTELLIGENCE
ENERGY AND NATURAL RESOURCES

United States Senate

WASHINGTON, DC 20510-0304

STATE OFFICES:
2200 EAST CAMELBACK ROAD
SUITE 120
PHOENIX, AZ 85016
(602) 840-1891

7315 NORTH ORACLE ROAD
SUITE 220
TUCSON, AZ 85704
(602) 575-8633

May 12, 1995

Congressional Liaison
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Congressional Liaison:

The attached communication is sent for your consideration. Please investigate the concerns expressed therein and forward me the necessary information for reply, returning the enclosed correspondence with your answer.

Thank you for your consideration.

Sincerely,

JON KYL
United States Senator

JK:tg

Enclosure

APPEARS THIS WAY
ON ORIGINAL

No. 95-4672

JON KYL
ARIZONA
702 HART SENATE OFFICE BUILDING
(202) 224-4521

COMMITTEES:
JUDICIARY
INTELLIGENCE
ENERGY AND NATURAL RESOURCES

United States Senate

WASHINGTON, DC 20510-0304

STATE OFFICES:
2200 EAST CAMELBACK ROAD
SUITE120
PHOENIX, AZ 85016
(602) 840-1891

7315 NORTH ORACLE ROAD
SUITE 220
TUCSON, AZ 85704
(602) 575-8633

May 12, 1995

Congressional Liaison
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Congressional Liaison:

The attached communication is sent for your consideration. Please investigate the concerns expressed therein and forward me the necessary information for reply, returning the enclosed correspondence with your answer.

Thank you for your consideration.

Sincerely,

/s/

JON KYL
United States Senator

JK:tg

Enclosure

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUL 10 1995

The Honorable Richard G. Lugar
United States Senate
Washington, D.C. 20510-1401

Dear Senator Lugar:

This is in response to your letter of June 9, 1995, on behalf of _____ regarding mifepristone (RU-486).

As you may know, in January 1993, the President directed the Secretary of Health and Human Services to assess initiatives to promote the testing of RU-486 and other antiprogestins in the United States. The Food and Drug Administration (FDA) is an active participant in this ongoing evaluation and is responsible for ensuring the safety and effectiveness of drugs approved for use in the United States.

As _____ mentioned, RU-486 is currently in clinical trials in this country. Roussel-Uclaf, the manufacturer of RU-486, has agreed to donate its United States patent rights for RU-486 to The Population Council, a non-profit organization, to permit the testing of RU-486 as an abortifacient in this country. Clinical testing of the drug in the United States will allow the collection of data on the drug, including information on how the drug could be used properly in this country; it will provide an opportunity to train doctors in the careful administration of the drug; and it will give American women who participate in the clinical trial access to the drug. You can be assured that the rights and welfare of these women will be protected in accord with FDA's regulations which require and set forth conditions for ensuring the protection of all human research subjects. The process that I have described is deliberative, scientific, and appropriately applied to this drug for this indication.

RU-486 has been marketed for non-surgical termination of pregnancies in France, the United Kingdom and Sweden. The drug is also under study for labor induction, contraception, Cushing's syndrome, endometriosis, meningioma and breast cancer.

We appreciate and respect your constituent's personal opinion on this issue. However, we hope that _____ will

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OLA	/S/	7/7/95						
HFA-7	/S/	7/7/95						

understand that our authority is limited to safety and efficacy requirements mandated by law. We cannot refuse testing or approval of a new drug if the data to support such actions are submitted to the Agency.

We hope this information is helpful. If we can be of further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

cc: HFW-10 (2)
HFW-14

R/D: :07/05/95
Edit: 07/06/95
F/T: 07/07/95
s:\wp ru-486.rgl
FDA Control No. 95 5526

APPEARS THIS WAY
ON ORIGINAL

RICHARD G. LUGAR
INDIANA

SH 306 SENATE OFFICE BUILDING
WASHINGTON, D.C. 20510
202-224-4814

United States Senate

WASHINGTON, DC 20510-1401

COMMITTEES:
FOREIGN RELATIONS
AGRICULTURE, NUTRITION AND FORESTRY
Chairman
SELECT COMMITTEE
ON INTELLIGENCE

June 9, 1995

Ms. Diane Thompson
Associate Commissioner for Legislative
Affairs (HFW-1)
FDA - 5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Thompson:

Because of the desire of this office to be responsive to all inquiries and communications, your consideration of the attached is requested.

Your findings and views, in duplicate form, along with the return of the enclosure, will be greatly appreciated. Please direct your reply to the attention of Darlee Williams of my Washington office.

Thank you for your thoughtful attention.

Sincerely,

Richard G. Lugar
United States Senator

RGL/cjl
Enclosure

APPEARS THIS WAY
ON ORIGINAL

No. 95-5526

BARBARA A. MIKULSKI
MARYLAND

SUITE 709
HART SENATE OFFICE BUILDING
WASHINGTON, DC 20510

(202) 224-4654
TDD: (202) 224-5223

United States Senate

WASHINGTON, DC 20510-2003

February 22, 1995

Ms. Diane Thompson
Assoc. Commissioner for Legislative Affs.
Dept. of Health & Human Services
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Thompson:

I am writing to request your consideration of the attached correspondence from _____ Please respond directly to _____ and send a copy to Pamela Nystrom of my staff.

Thank you for your assistance.

Sincerely,

Barbara A. Mikulski

Barbara A. Mikulski
United States Senator

BAM:pin
Enclosure

APPEARS THIS WAY
ON ORIGINAL

95-1796

SUITE 283
WORLD TRADE CENTER
BALTIMORE, MD 21202-3041

SUITE 202
60 WEST STREET
ANNAPOLIS, MD 21401-1933

SUITE 208
9658 BALTIMORE AVENUE
COLLEGE PARK, MD 20740-1346

SUITE 301
82 WEST WASHINGTON STREET
HAGERSTOWN, MD 21740-4804
(301) 797-2826

CITY CENTER ON THE PLAZA
213-219 WEST MAIN STREET
SALISBURY, MD 21801
(410) 546-7711

SPECIAL

Memorandum

March 8, 1995

Note to: [redacted] - ok 3/10
[redacted] - ok 3/10 per e-mail
[redacted] - ok 3/13
[redacted] - ok 3/10
[redacted]
[redacted]

Subject: Citizen Petition on Mifepristone - ACTION

As you are aware, [redacted] has asked me to draft a response to the mifepristone petition, to obtain your comments, and to synthesize all comments into a response that we can all review. She has also asked that we respond to this petition as soon as possible.

Attached is a draft response for your review. Please provide your comments/concurrence to me by close of business on Monday, March 13. If you need a copy of the petition (it is lengthy), please let me know as soon as possible. Thank you.

/S/

[redacted]
[redacted]
Parklawn Building, Room [redacted]
Telephone: [redacted]
Fax: [redacted]

Attachment

cc: [redacted]

My comments are attached.

/S/

Thanks

APPEARS THIS WAY
ON ORIGINAL

o: [redacted]@EXECSEC@FDAOC
c: [redacted]@EXTAFFAIRS@FDAOC
cc:
rom: [redacted]@EXTAFFAIRS@FDAOC
ubject: Mifepristone Petition
ate: Friday, March 10, 1995 10:44:21 EST
ttach:
ertify: N
orwarded by:

[redacted]

[redacted] and I think your letter is absolutely perfect. In this case, less is definitely more. This note constitutes our comments and concurrence.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

To: [redacted] EXECSEC@FDAOC
Cc: SSWGATE@FDA-SSW@Servers[FDACD [redacted]
SSWGATE@FDA-SSW@Servers[FDACD.. [redacted]
SSWGATE@FDA-SSW@Servers[FDACD. [redacted]
Bcc:
From: [redacted]
Subject: RE: Petition on mifepristone
Date: Friday, March 10, 1995 at 10:53:00 am
Attach:
Certify: N
Forwarded by:

I believe that your draft letter provides an appropriate response to the petition. However, in the past, this office usually addressed each issue in the petition as recommended by GC.

APPEARS THIS WAY
ON ORIGINAL

To: [redacted]@EXECSEC@FDAOC
Cc: SSWGATE@FDA-SSW@Servers[FDACD [redacted]
[redacted]@EXTAFFAIRS@FDAOC
SSWGATE@FDA-SSW@Servers[FDACD [redacted]
[redacted]@OGC.FDA@FDAOC, [redacted]@OGC.FDA@FDAOC
Bcc:
From: [redacted]@IO@FDAOC
Subject: Petition on mifepristone
Date: Monday, March 6, 1995 12:00:45 EST
Attach:
Certify: N
Forwarded by:

As you all have heard, we have received a citizens petition asking us variously to either completely approve any NDA for mifepristone as an abortafacient, or to only approve it if it is safe and effective for that use. There are other, [redacted] side issues, such as whether we should use foreign data.

I would like to get this petition off of our plate --

[redacted]

[redacted] - I'd appreciate if if you would take a first crack at a petition response, and send it through clearance. Everyone can give their views directly to you, and you can synthesize them into something we can all look at.

Thank you very much.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

LAW OFFICES
McKENNA & CUNEO
1575 EYE STREET, N.W.
WASHINGTON, D.C. 20005
(202) 789-7500
CABLE ADDRESS: MCKENCOUN WASHDC
TELEX (710) 710-822-0148
FAX (202) 789-7804

LOS ANGELES
444 SOUTH FLOWER STREET
LOS ANGELES, CALIFORNIA 90071
(213) 688-1000

SAN FRANCISCO
STEUART STREET TOWER
ONE MARKET
SAN FRANCISCO, CALIFORNIA 94105
(415) 267-4000

SAN DIEGO
SUITE 2600, SYMPHONY TOWERS
750 B STREET
SAN DIEGO, CALIFORNIA 92101
(619) 233-5400

DENVER
SUITE 4800
370 SEVENTEENTH STREET
DENVER, COLORADO 80202
(303) 634-4000

DALLAS
3700 BANK ONE CENTER
717 MAIN STREET
DALLAS, TEXAS 75201
(214) 748-5700

BRUSSELS
AVENUE LOUISE 207, BOX 7
B-1050 BRUSSELS
BELGIUM
011 (322) 640-4040

February 28, 1995

By Hand Delivery

Dockets Management Branch (HFA-305)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
Room ——
12420 Parklawn Drive
Rockville, MD 20852

CITIZEN PETITION

Petitioners, Hon. Thomas J. Bliley, Jr. (Chairman, Committee on Commerce); Hon. J. Dennis Hastert (Committee on Commerce); Hon. Cliff Stearns (Committee on Commerce, Committee on Veterans Affairs); Hon. Jack Fields (Committee on Commerce); Hon. Paul E. Gillmor (Committee on Commerce); Hon. Henry Hyde (Chairman, Committee on the Judiciary); Hon. Ed Bryant (Committee on the Judiciary, Committee on Agriculture); Hon. Bill Barrett (Committee on Economic and Educational Opportunities, Committee on Agriculture); Hon. Jim Talent (Committee on Economic and Educational Opportunities); Hon. Steve Largent (Committee on Science); Hon. Duncan Hunter (Committee on National Security); Hon. Mike Parker (Committee on the Budget); Hon. Jim Bunning (Committee on the Budget); Hon. John Murtha (Committee

LAW OFFICES
McKENNA & CUNEO

on Appropriations); Hon. Barbara Vucanovich (Committee on Appropriations); Hon. Jim Lightfoot (Committee on Appropriations); Hon. Enid G. Waldholtz (Committee on Rules); Hon. Nick J. Rahall, II(Committee on Resources, Committee on Transportation and Infrastructure); Hon. Christopher H. Smith (Committee on International Relations, Committee on Veterans' Affairs); Hon. Andrea Seastrand (Committee on Science, Committee on Transportation and Infrastructure); Hon. Todd Tiahrt (Committee on National Security); Hon. Linda A. Smith (Committee on Resources, Committee on Small Business); Hon. Dan Coats (Committee on Labor and Human Resources); and the following individuals: Laurence M. Demers, M.D.; Camilla Hersh, M.D.; Donna J. Harrison, M.D.; Earle W. Lingle, Ph.D.; Eugene F. Diamond, M.D.; J. Walter Sowell, Ph.D.; and Joel Brind, Ph.D., hereby submit this citizen petition ("petition") under section 701 of the Federal Food, Drug, and Cosmetic Act ("the FDCA or Act"), 21 U.S.C. § 371 (1988 & Supp. V 1993), and its implementing regulations, 21 C.F.R. §§ 10.25 and 10.30 (1994). Petitioners specifically request that the Commissioner of the Food and Drug Administration ("the Commissioner") refuse to approve any new drug applications ("NDA") submitted pursuant to section 505(b) of the Act, 21 U.S.C. § 355(b) (1988), for RU 486 (mifepristone) for use as a pharmaceutical abortifacient.1/

1/ The comments submitted herein are limited to RU 486 as an abortifacient drug product. This petition does not, therefore, oppose or address in any manner the use of RU 486 in the treatment of diseases, such as breast cancer or meningiomas (brain tumors).

LAW OFFICES
McKENNA & CUNEO

A. ACTION REQUESTED

Petitioners request that the Commissioner refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials. The basis for petitioners' request is the statutory mandate of the Food and Drug Administration ("FDA") to withhold approval of any NDA that lacks sufficient data to establish that a drug is safe and effective for its intended use.[2/] Approval of any NDA that is devoid of the appropriate safety and effectiveness data would not only be an express violation of the FDCA, but also an arbitrary and capricious agency action.

Petitioners also are concerned that RU 486 could be approved in the United States ("U.S.") based largely on foreign data, with only limited safety data generated from studies conducted in the U.S. Because approval based on possibly invalid foreign data and limited safety data would expose patients to significant and unreasonable adverse health risks, petitioners respectfully request that FDA consider the following factors in reviewing any NDA for RU 486.

- Foreign data that has not undergone a validation review by FDA may be unreliable.
- Because of the gravity of the potential risks of RU 486, it is imperative that all safety concerns in the potential populations affected by RU 486 be adequately addressed by NDA-generated data.

2/ See FDCA § 505(d), 21 U.S.C. § 355(d).

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- Adequate directions for use of RU 486 cannot be provided in approved product labeling, unless direct safety/effectiveness issues are sufficiently resolved and defined by reliable scientific research.

- Unlike treatment for Acquired Immunodeficiency Syndrome ("AIDS"), advanced metastatic refractory cancers or other severely debilitating life-threatening diseases, alternatives to the RU 486/prostaglandin ("RU 486/PG") abortion method are currently available in the U.S. Because alternative abortion methods exist, no novel or urgent medical situation is present that requires FDA to expedite review or approval of an NDA for RU 486 as an abortifacient.

- The availability of alternative abortion methods should be considered by FDA in performing a risk/benefit evaluation of RU 486 as an abortifacient.

In light of these considerations, petitioners specifically request that:

(1) FDA audit all foreign data submitted in support of any NDA for RU 486 as an abortifacient;

(2) No NDA for RU 486 as an abortifacient be approved by FDA unless the safety and efficacy concerns presented in this petition are adequately resolved;

(3) FDA not approve RU 486 in the absence of clinical and nonclinical data that fully evaluate the potential adverse effects on the health of women who take RU 486 and/or misoprostol and any children born after exposure to these drugs;

(4) FDA refrain from adjusting and/or expediting the NDA approval process for any NDA for RU 486 for such use;

(5) In the event that FDA determines that an NDA for RU 486 meets the stringent statutory and regulatory application requirements, the approved conditions for use should be strictly limited. In particular, the drug product's labeling should bear adequate directions for use, and complete contraindication, complication and adverse reaction information. In addition, the drug product should be accompanied by an approved patient package insert. The labeling further should provide that

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administration of the drug must be limited to patients that are under the direct supervision and care of licensed physicians practicing in ambulatory care facilities or hospitals that meet the standards of the Joint Commission on Accreditation of Healthcare Organizations.

B. STATEMENT OF GROUNDS

This petition concerns FDA's statutory obligation to approve only those NDAs that contain adequate evidence that the proposed drug is safe and effective for its intended use. Because there appear to be a number of unresolved safety and/or effectiveness questions associated with RU 486, FDA is statutorily obligated to withhold approval of any NDA for RU 486, a potentially harmful and toxic drug product.

1. FDA's Statutory Mandate

Specifically, section 505(b)(1)(A) of the FDCA requires that an applicant submit as part of an NDA, full reports of investigations that establish a drug is safe and effective for its intended use.[3/]

a) FDA May Only Approve An NDA That Demonstrates Drug Safety

Section 505(d) indirectly defines the necessary safety evidence to support approval of an NDA. This section provides, in relevant part, that FDA must refuse to approve any NDA that does not include: (1) "*adequate tests by all methods reasonably applicable* to

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show whether the drug is safe for use" under its labeled conditions,[4] or (2) *sufficient information* to determine whether the drug is safe for use under the labeled conditions.[5] Petitioners assert that a reasonable interpretation of these statutory requirements is that safety data on *all segments of the population affected* by the administration of the drug must be provided before FDA may lawfully approve RU 486.

The segments of the population affected by RU 486 include the aborting women and their subsequent born children.[6] Petitioners are unaware of any published data on the effects of RU 486 on subsequent born children, and have identified only minimal data on certain potential health risks to users, such as the risk of breast cancer after induced abortion. Absent full reports of such critical data, FDA has a statutory obligation to refuse to approve an NDA for RU 486 as an abortifacient.

Because the agency has limited statutory authority to require controlled post-marketing studies, FDA relies on premarket research to evaluate the risk/benefit ratio of a drug and its potential post-approval risks. Prescribing physicians and the general public therefore depend on premarket trials as the source of reliable information on a new drug. FDA should require such data on RU 486 with regard to all population segments. Sufficient safety data is required not only for FDA to approve the drug, but

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4/ See FDCA § 505(d)(1) (emphasis added), 21 U.S.C. § 355(d)(1).

5/ See FDCA § 505(d)(4) (emphasis added), 21 U.S.C. § 355(d)(4).

6/ The phrase "subsequent born children" is defined for the purpose of this document as children born as a result of a pregnancy continued after a failed RU 486 abortion as well as any additional children conceived and born after exposure to RU 486.

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also to (1) develop adequate directions for use of RU 486 as an abortifacient; (2) provide physicians with safety and efficacy information so that they may prescribe an optimal abortion regimen; and (3) provide sufficient information to assist patients in making well-informed medical decisions.

b) FDA May Only Approve An NDA Supported By Substantial Evidence Of Effectiveness

Section 505(d)(5) provides, in relevant part, that FDA must refuse to approve an NDA when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[7] Section 505(d) defines "substantial evidence" to mean evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.[8] In defining "substantial evidence," FDA has stated that a showing of *clinically significant* evidence of effectiveness is required.[9] Further, the Supreme Court has recognized that substantial evidence of effectiveness necessarily entails a showing of *some benefit* to the patient.[10] Petitioners therefore assert that an NDA applicant for RU 486 must establish that the drug product is

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7/ ... 21 U.S.C. § 355(d)(5).

8/ 21 U.S.C. § 355(d).

9/ See Warner-Lambert Co. v. Heckler, 787 F.2d 147, 155 (1986).

10/ See United States v. Rutherford, 442 U.S. 544, 553 n.9 (1979); Warner-Lambert Co. v. Heckler, 787 F.2d at 155 (discussing United States v. Rutherford).

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clinically effective as an abortifacient. Without such evidence, FDA may not lawfully approve the NDA.

2. Foreign Data Must Comport With U.S. Standards To Support NDA Approval

FDA regulations require foreign clinical studies submitted by an NDA applicant to be well-designed, well-conducted, and performed by qualified investigators. The trials also must be conducted in accordance with ethical principles acceptable to the world community, or the foreign country's standards.[11/] Additionally, foreign clinical data must be applicable to the U.S. population and U.S. medical practice, and validated through on-site inspections and/or submissions of case records or additional background data and information.[12/] Foreign clinical data that fails to meet the above criteria cannot be accepted by the agency in support of drug approval.

Aware that most of the available data on RU 486 has been generated to secure foreign approvals, petitioners are concerned that an NDA applicant may attempt to rely on this data to support U.S. approval. Because foreign clinical trials may not have been conducted under adequate and well-controlled conditions, and/or under conditions that are representative of the U.S. population of potential RU 486 users, the agency should carefully examine the origin, design and patient population of each foreign trial proffered by an NDA applicant to support approval of RU 486. The agency also should conduct in-

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11/ See 21 C.F.R. §§ 312.120, 314.106 (1994).

12/ See 21 C.F.R. § 314.106 (1994).

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depth validity audits of each foreign clinical trial relied upon by an RU 486 NDA applicant. Only those clinical trials that comport with all statutory and regulatory requirements may lawfully be considered by the agency to support approval of RU 486. Petitioners believe that some or all of the known foreign clinical data may not comport with U.S. standards[13] and, therefore, any NDA which relies in whole or in part upon foreign studies most likely will fail to meet the substantial evidence standard.

3. **FDA Should Deny Approval Unless Safety/Effectiveness Concerns Are Adequately Resolved**

a) **RU 486 Alone Is Ineffective And Poses Significant Adverse Effects, Complications, And Potential Risks**

As a single-entity abortifacient, RU 486 is relatively ineffective.[14] There is a high incidence of incomplete abortions[15] and ongoing pregnancies[16] when RU 486

13/ Dr. Meredeth Turshen has raised concerns about the accuracy of the complication and failure rates being reported by foreign studies funded by Roussel Uclaf (the French manufacturer of RU 486), in light of the results that have been obtained by some independant researchers, which have not been published. Dr. Turshen was a fellow at INSERM (the French equivalent of NIH) during 1989-90. See Comments by Dr. Turshen at "Contraceptive Technology: Promises and Politics" workshop at the annual meeting of the Am. Public Health Assoc. (Oct. 2, 1990); "Researcher suggests side effects of RU-486 may be underreported" Am. Medical News, Oct. 26, 1990, at 8; Boston Herald, July 31, 1992, at 25.

14/ An average value for the frequency of complete abortion with RU 486 alone is approx. 63%. WHO Task Force On Post-Ovulatory Methods For Fertility Regulation, Termination Of Early Human Pregnancy With RU 486 (Mifepristone) And The Prostaglandin Analogue Sulprostone: A Multi-Centre, Randomized Comparison Between Two Treatment Regimens, 4 Hum. Reprod. 718, 719 (1989) (hereafter "WHO Task Force, 1989"). See Table 1 for comprehensive statistics on complete abortion rates.

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is used during the first seven weeks of gestation. An even higher failure rate is observed in patients with greater body mass.17/ Incomplete abortion requires surgical intervention.18/ Incomplete abortions can also cause complications such as heavy bleeding and intrauterine infection, and may lead to pelvic inflammatory disease and infertility.19/ Further, when a pregnancy was continued after

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15/ Grimes, Mifepristone (RU 486) For Induced Abortion, 3 Women's Health Issues 171, 172 (1993) (hereafter "Grimes, 1993"); Grimes, et al., Early Abortion With A Single Dose Of The Antiprogestin RU-486, 158 Am. J. Obst. Gyn. 1307, 1308 (1988) (hereafter "Grimes, et al., 1988") (10% failure with 600 mg dose in women less than or equal to 49 days from last menstrual period ("LMP")); and Shoupe, et al., Pregnancy Termination With A High And A Medium Dosage Regimen Of RU 486, 33 Contraception 455 (1986) (hereafter "Shoupe, et al., 1986") (90% failure in high dose group -- 400 mg/day for 4 days (N=5) or 200 mg/day for 4 days (N=5) -- all women within 49 days of first day of LMP). For statistics on incomplete abortion rates, see Table 2.

16/ With RU 486 alone, from 8.3% to 46.3% of pregnancies continue. See Table 9 for reported statistics.

17/ Grimes, et al., found that the risk of failure from RU 486 alone for women in the largest body mass group studied was 2.9 times greater than that of women in the lowest body mass group studied. Grimes, et al., Predictors Of Failed Attempted Abortion With The Antiprogestin Mifepristone (RU 486), 162 Am. J. Obst. Gyn. 910, 913-14 (1990) (hereafter "Grimes, et al., 1990") (risk with a Quetelet's index [weight(kg)/height(m2)] greater than 23.81 was 2.9 times the risk with index less than 20.25); see also Grimes, 1993, at 172 (1993). See discussion *infra* Section 3.d.

18/ See Chan, et al., Blood Loss In Termination Of Early Pregnancy By Vacuum Aspiration And By Combination Of Mifepristone And Gemeprost, 47 Contraception 85 (1993) (hereafter "Chan, et al., 1993") (medical termination of pregnancy carries risk of incomplete abortion that requires surgical intervention).

19/ See Raymond, et al., RU 486: Misconceptions, Myths And Morals 38 (1991) (hereafter "Raymond, et al., 1991") ("Incomplete abortions . . . necessitate that the products of conception are removed by conventional abortion methods. Incomplete

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unsuccessful RU 486 administration, one child had severe deformities[20] including sirenomelia, a cleft palate and lip, micrognathia and hygroma.[21] Sirenomelia is a rare congenital malformation in which the lower extremities are fused.

As stated, one of the serious side effects of RU 486 is:

> the occurrence of excessive bleeding, requiring emergency curettage and sometimes blood transfusion. From published data it would appear that the risk of this complication is [approx.] 1-2% when RU 486 is used alone.[22/23]

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evacuation can be accompanied by severe bleeding. . . . This adverse effect of RU 486/PG abortion may lead to . . . pelvic inflammatory disease (PID) from infection, to infertility, and possibly uterine cancer.") For statistics on the incidence of infection with pharmaceutical abortion, see Table 8.

20/ See Pons, et al., Development After Exposure To Mifepristone In Early Pregnancy, 338 Lancet 768 (1991) (hereafter "Pons, et al., 1991") (although the researchers couldn't determine whether the abnormalities were related to RU 486, they concluded that "a deleterious effect of mifepristone cannot be ruled out."). See also *infra* Section 4.b.(1) and accompanying footnotes.

21/ Micrognathia is an abnormality characterized by smallness of the jaw, especially the underjaw. Stedman's Medical Dictionary 875 (5th ed. 1982). Hygroma is a cystic swelling, usually of the neck area, containing serous fluid. See Stedman's Medical Dictionary 668 (5th ed.); Dorland's Illustrated Medical Dictionary 789 (28th ed. 1994).

22/ Swahn, et al., Effect Of Oral Prostaglandin E2 On Uterine Contractility And Outcome Of Treatment In Women Receiving RU 486 (Mifepristone) For Termination Of Early Pregnancy, 4 Hum. Reprod. 21, 27 (1989) (hereafter "Swahn, et al., 1989"). See also, Zheng Shu-rong, RU 486 (Mifepristone): Clinical Trials In China, 149 Acta Obst. Gyn. Scand. Suppl. 19 (1989) (hereafter "Zheng Shu-rong, 1989") (4 patients (1.34%) suffered heavy bleeding, necessitating emergency curettage after receiving RU 486); The RU 486 Collaboration Group, Termination Of Early Pregnancy By RU 486 Alone Or In Combination With Prostaglandin, 25 Chinese J. Obst. & Gyn. 31 (1990) (clinically significant [177.4 ml] mean blood loss after complete abortion reported).

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This has led researchers to conclude that the risk of heavy bleeding is a serious complication that necessitates easy access to a hospital.[24]

b) RU 486 In Combination With Misoprostol Presents Separate Risks And Safety Concerns

When used in a two-step procedure with misoprostol, a prostaglandin, the abortifacient rate of RU 486 has been shown to increase.[25] U.S. test protocols generally

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23/ Researchers have noted that the total amount of blood lost by women treated with RU 486 is not reduced with a RU 486/PG regimen. Swahn, et al., 1989, at 27 (1989); Rodger & Baird, Blood Loss Following Induction Of Early Abortion Using Mifepristone (RU 486) And A Prostaglandin Analogue (Gemeprost), 40 Contraception 439 (1989) (hereafter "Rodger & Baird, 1989"); Cameron, et al., Therapeutic Abortion In Early Pregnancy With Antiprogestogen RU 486 Alone Or In Combination With Prostaglandin Analogue (Gemeprost), 34 Contraception 459 (1986). But see, Zheng Shu-rong, 1989 (reporting a lower volume of blood loss with RU 486/PG regimen [52 ml (RU 486/PG) v. 117 ml (RU 486)] in women who aborted within 49 days amenorrhea).

24/ Thong & Baird, Induction Of Abortion With Mifepristone And Misoprostol In Early Pregnancy, 99 Br. J. Obst. Gyn. 1004, 1006 (1992) (hereafter "Thong & Baird, 1992"). See also Couzinet, et al., Termination Of Early Pregnancy By The Progesterone Antagonist Ru 486 (Mifepristone), 315 N. Eng. J. Med. 1565, 1569 (1986); Sitruk-Ware, et al., The Use Of The Antiprogestin RU 486 (Mifepristone) As An Abortifacient In Early Pregnancy - Clinical And Pathological Findings; Predictive Factors For Efficacy, 41 Contraception 221, 239-40 (1990); El-Refaey & Templeton, Early Induction Of Abortion By A Combination Of Oral Mifepristone And Misoprostol Administered By The Vaginal Route, 49 Contraception 111, 113-14 (1994) (hereafter "El-Refaey & Templeton, 1994"); Rodger & Baird, 1989, at 444; UK Multicentre Trial, The Efficacy And Tolerance Of Mifepristone And Prostaglandin In First Trimester Termination Of Pregnancy, 97 Br. J. Obst. Gyn. 480, 485 (1990) (hereafter "UK Multicentre Trial, 1990"); Chan, et al., 1993, at 85; Wu, et al., Clinical Trial On Termination Of Early Pregnancy With Ru 486 In Combination With Prostaglandin, 46 Contraception 203, 209 (1992) (hereafter "Wu, et al., 1992").

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use a 600 mg dose of RU 486 followed by 400 ug of misoprostol administered orally. However, three major issues have arisen with respect to the safety and effectiveness of this particular combination. First, researchers found that despite the increase in effectiveness demonstrated over RU 486 as a single entity, the effectiveness of the two-drug combination declines significantly after the 7 week gestation period. In women less than or equal to 49 days amenorrhea, the complete abortion rate is 97.5%.[26] This rate drops to 89.1% in women at 50-63 days, and 84.4% in women at 57-63 days.[27] As a result, researchers have concluded that the combination of RU 486 (200 or 600 mg) and oral misoprostol (600 ug) is effective for inducing abortion only in women of less than 50 days amenorrhea. At gestations greater than 56 days, "this combination may result in too many incomplete abortions to be clinically acceptable."[28]

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25/ For statistics on complete abortion rates using RU 486 alone, see Table 1 (average complete abortion rate [approx.] 63%); compare to complete abortion rates of 84.4% to 99% using RU 486/oral or vaginal misoprostol up to 63 days amenorrhea (Table 4). Complete abortion rates of 75.3% to 99% using RU 486 in combination with other prostaglandins up to 63 days amenorrhea are reported in Table 5.

26/ McKinley, et al., The Effect Of Dose Of Mifepristone And Gestation On The Efficacy Of Medical Abortion With Mifepristone And Misoprostol, 8 Hum. Reprod. 1502 (1993) (hereafter "McKinley, et al., 1993") (regimen of either 200 or 600 mg RU 486 followed by 600 ug misoprostol 48 hrs. later).

27/ Id.

28/ Id. at 1502. See also Ulmann, Warning On Low Dose Mifepristone Use, 6 PharmacoEconomics 90 (1994) ("Currently available information suggests that the efficacy of misoprostol following mifepristone is significantly lower in pregnancies above 49 days of amenorrhea. The efficacy rate drops to only 90% for pregnancies between 49 and 63 days of amenorrhea, a value that is medically unacceptable.").

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Second, approximately thirty percent of patients do not abort the embryo prior to leaving the clinic or hospital (four hours after misoprostol administration).29/ This occurs because the pharmacological lag time for misoprostol may exceed the normal four-hour monitoring period of a typical medical abortion protocol. This is a serious public health concern since "the majority of women experience some pain during the passage of the fetus and heavy bleeding requiring resuscitation is most likely to occur at this time."30/

Third, researchers in a British study found that the RU 486/oral misoprostol combination results in a higher incidence of ongoing pregnancies (4% of 121 subjects) than RU 486 followed by other prostaglandins, such as gemeprost or sulprostone (0.2%).31/ The results of that study are supported by the outcome of a large, clinical

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29/ Aubeny & Baulieu, Contragestion With RU 486 And An Orally Active Prostaglandin, 312 C.R. Acad. Sci. Paris (III) 539 (1991) (31%); Thong & Baird, 1992 (21%); Peyron, et al., Early Termination Of Pregnancy With Mifepristone (RU 486) And The Orally Active Prostaglandin Misoprostol, 328 N. Eng. J. Med. 1509 (1993) (hereafter "Peyron, et al., 1993") (33.2% in study 1 and 25.4% in study 2); McKinley, et al., 1993 (36.4% and 26.4% in the two groups given 200 or 600 mg RU 486); Thong, et al., What Do Women Want During Medical Abortion?, 46 Contraception 435 (1992) (hereafter "Thong, et al., 1992") (29%).

30/ Thong, et al., 1992, at 440.

31/ See Thong & Baird, 1992, at 1006, reporting:

> The 8% incidence of ongoing pregnancies with this regimen is slightly higher than that reported using a combination of mifepristone with gemeprost or sulprostone (Sylvestre et al. 1990; UK Multicentre Trial, 1990). We have previously reported ongoing pregnancies in two out of 21 women (up to 56 days amenorrhea) who were given 200 mg mifepristone followed by

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investigation in France. The results of the French study, which analyzed the effectiveness of RU 486/oral misoprostol in 488 women (study 1), confirmed that the ongoing pregnancy rate with 400 ug oral misoprostol is four times higher (four women, 0.8%) than that found in Britain using gemeprost (1 woman, 0.2%).32/ In conclusion, although misoprostol increases the abortion rate for RU 486, its introduction into an abortion regimen still presents considerable risks and safety concerns for the pregnant woman.

As discussed in more detail below, the use of prostaglandin analogs presents additional safety risks to the woman as compared to RU 486 used as a single-agent abortifacient.

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> 200 ug and 400 ug of misoprostol (Norman et al. 1991). Therefore, in a consecutive series of 121 women treated with mifepristone and misoprostol in our centre, the ongoing pregnancy rate was 4% (95% CL 0.6-8.6%). In a consecutive series of 470 pregnancies (<56 days) terminated with mifepristone (50-600 mg) and gemeprost (0.5 mg-1 mg) in our institution, there has been only one ongoing pregnancy (0.2%). If the higher incidence of ongoing pregnancies is confirmed by a larger study, . . . , the clinical usefulness of this combination of mifepristone and oral misoprostol for routine clinical use would be in doubt.

Two other British researchers reported a 3% (5 patients) ongoing pregnancy rate in a series of 150 patients receiving oral misoprostol 800 ug after 200 mg RU 486. El-Refaey & Templeton, 1994, at 112.

32/ Peyron, et al., 1993.

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c) **RU 486/PG: Increases Severity Of Adverse RU 486 Effects And Presents Separate Complications**

Even if effectiveness was not an issue in the use of RU 486 and misoprostol, prostaglandins are known to intensify the uterine cramping and pelvic pain associated with abortion to a point requiring administration of narcotics.[33] Prostaglandins can also cause severe gastrointestinal complications.[34] In addition, life-threatening cardiovascular complications can result from prostaglandin use, including death.[35] Two

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33/ For data on RU 486/oral misoprostol abortion, see Table 6 (pain reported in from 79.1 to 85% patients; analgesia needed in from 12.5 to 57.1% patients). For data reported for RU 486 with other prostaglandins, see Table 7. See also WHO, Pregnancy Termination With Mifepristone And Gemeprost: A Multicenter Comparison Between Repeated Doses And A Single Dose Of Mifepristone, 56 Fertility & Sterility 32, 39 (1991) (hereafter "WHO, 1991") ("As anticipated, mifepristone-induced uterine contractions and vaginal bleeding were associated with lower abdominal pain, which became almost universal after gemeprost administration."); UK Multicentre Trial, 1990, at 484 (where 16% reported mild, moderate or severe pain the first 24 hours after mifepristone compared to 84% who reported pain 2 hours after gemeprost); Thong & Baird, 1992, at 1005 (11% reported abdominal pain before misoprostol administration and 85% 2 hours afterwards); McKinley, et al., 1993, at 1504 (53.6% reported abdominal pain before misoprostol administration and 79.1% 2 hours afterwards).

34/ Zheng Shu-rong, 1989, at 22 (reporting a higher incidence of abdominal pain resulting from uterine cramping and diarrhea in women given RU 486 plus a PG); Thong & Baird, 1992, at 1005-06 (reporting an expected increase in PG-related side effects 2 hrs. following administration of misoprostol, including vomiting, pain, faintness and diarrhea); McKinley, et al., 1993, at 1504 (reporting increases in vomiting, pain, diarrhea and fainting 2 hrs. after taking misoprostol); UK Multicentre Trial, 1990, at 484 (where 3% and 0.5% reported vomiting and diarrhea during the first 4 hours after mifepristone compared to 26% and 13% during the first 4 hours after gemeprost). See also Sacha, A., Abortion Pills on Trial, Time, Dec. 5, 1994, at 45-46.

35/ See Ulmann, et al., Medical Termination Of Early Pregnancy With Mifepristone (RU 486) Followed By A Prostaglandin Analogue, 71 Acta Obst. Gyn. Scand. 278 (1992)
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common effects of prostaglandins are a decrease in pulse rate[36] and low blood pressure which may lead to cardiac arrest. One study reported a slight decrease in the mean systolic and diastolic blood pressure four hours after misoprostol administration.[37] In addition, six women (1.2%) had "a substantial but transient decrease in blood pressure" (the systolic blood pressure fell by more than 30 mm Hg and the diastolic blood pressure by more than 15 mm Hg).[38] Although transient, this is clinically significant hypotension, an adverse event that should be carefully examined.

d) Special Patient Populations Present Unique Risks

Because of common pre-existing conditions and disease states, RU 486 may never be a safe and effective abortifacient for certain patients. Specifically, RU 486/PG

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(hereafter "Ulmann, et al., 1992") (reporting 3 myocardial infarctions (1 fatal) and 3 cases of severe hypotension after sulprostone injection); Anonymous, A Death Associated With Mifepristone/Sulprostone, 337 Lancet 969 (1991) (discussing the same death reported in Ulmann, et al., 1992). See also Institute of Medicine, Clinical Applications Of Mifepristone (RU 486) And Other Antiprogestins 27 (1993) (hereafter "Institute of Medicine, 1993") (reporting one patient death during the first trial of RU 486 with oral misoprostol).

36/ WHO Task Force On Post-ovulatory Methods Of Fertility Regulation, Termination Of Pregnancy With Reduced Doses Of Mifepristone, 307 BMJ 532 (1993) (hereafter "WHO Task Force, 1993") (reported significant decrease in pulse rate during the first few hours after gemeprost (3-4 beats/min.)); WHO, 1991 (reported significant ($P<0.001$) decrease in pulse rate during 4-hour period after gemeprost).

37/ Peyron, et al., 1993, at 1511.

38/ Id. (researchers attributed the hypotension to a vagal reaction secondary to painful uterine cramps).

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abortion poses substantial adverse risks to women with: asthma, epilepsy, diabetes, glaucoma, adrenal insufficiency, kidney disease, liver disorder, pulmonary disorder, cardiovascular disease, gastrointestinal disorders or intestinal disease, addisonian crisis susceptibility, prior use of steroid medication, prior use of some non-steroidal, anti-inflammatory medications like aspirin, recent use of hormonal contraception or presence of an IUD, recent Cesarean section, anemia, sickle cell anemia, hematologic or coagulation disorders, evidence of threatened abortion or ongoing spontaneous miscarriage, ectopic pregnancy, uterine fibroids or uterine anomalies.[39]

Other women may be subject to a greater risk of adverse reactions with medical abortion because of a "higher incidence" of complicating conditions. Four population segments may be at increased risk from this abortion method. The first population segment is African-American women. African-American women have a higher incidence of uterine fibroids than Caucasian women.[40] Thus, they may be at greater risk of retained products of conception. In cases where submucous uterine fibroids are present, these women may be at greater risk of excessive bleeding and related complications.

The second population segment is composed of Native-American (American Indians and Alaskan Natives) and Mexican-American women. These women have a

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39/ This list is based on expert review of the medical literature cited in Attachment 2.

40/ Wilcox, et al., Hysterectomy In The United States, 1988-1990, 83 Obst. & Gyn. 549 (1994) (fibroid tumor was reported as the primary diagnosis for 61% of African-American women and 29% of Caucasian women having hysterectomy); Kjerulff, et al., Hysterectomy And Race, 82 Obst. & Gyn. 757 (1993) (in study of more than 53,000 hysterectomies, African-American women were more than twice as likely to have a diagnosis of uterine fibroids as Caucasian women).

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much higher incidence of diabetes than that of the general U.S. population.41/ Consequently, Native-American and Mexican-American women with diabetes may be subject to a greater risk of complications from the gastrointestinal side effects of RU 486/PG abortion, such as loss of appetite, nausea, vomiting, and diarrhea. These side effects, although not severe in the average healthy American woman, are much more debilitating and may progress to more severe complications in a diabetic. Also, because Native-American women present more commonly with non-insulin dependent diabetes, their diabetic condition may be latent and remain undetected at the time of RU 486 administration.

Obese women present the third population segment. Grimes, et al., 1990 found that the risk of failure of RU 486 as a single agent abortifacient was 2.9 times greater for obese women than for women in the lowest body mass group studied. As a result, the researchers concluded that more pharmacokinetic research should be conducted to determine optimal dosing, which may not be the same for all patients.42/ The observation that obesity adversely affects RU 486 efficacy also was reported in a WHO

41/ Gohdes, et al., Diabetes In American Indians, 16 Suppl. 1 Diabetes Care 239 (1993); Gohdes, Diabetes In American Indians: A Growing Problem, 9 Diabetes Care 609 (1986); Freeman, et al., Diabetes In American Indians Of Washington, Oregon, And Idaho, 12 Diabetes Care 282 (1989); Knowler, et al., Diabetes Mellitus In The Pima Indians: Incidence, Risk Factors And Pathogenesis, 6 Diabetes/Metabolism Reviews 1 (1990); Knowler, et al., Diabetes Incidence And Prevalence In Pima Indians: A 19-Fold Greater Incidence Than In Rochester, Minnesota, 108 Am. J. Epidem. 497 (1978); Gardner, et al., Prevalence Of Diabetes In Mexican Americans--Relationship To Percent Of Gene Pool Derived From Native American Sources, 33 Diabetes 86 (1984); Carter, et al., Diabetes Mortality Among New Mexico's American Indian, Hispanic, And Non-Hispanic White Populations, 1958-1987, 16 Suppl. 1 Diabetes Care 306 (1993).

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study of RU 486 with sulprostone. The WHO study reported that subjects for whom the method failed were significantly heavier than those for whom the method resulted in complete abortion.[43] Heavier women also appear to have an earlier onset of bleeding.[44]

The fourth population segment is Asian-American women. These females may be at an increased risk of heavy bleeding and associated complications following RU 486/PG abortion.[45] Researchers to date have not conclusively identified the cause of the greater blood loss in this group of women.

The only potential population segment for whom RU 486/PG abortion might reach an acceptable level of safety is healthy women between the ages of 18 and 35,[46] who are

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[42] Grimes, et al., 1990, at 913-14 (risk with a Quetelet's index [weight(kg)/height(m2)] greater than 23.81 was 2.9 times the risk with index less than 20.25); see also Grimes, 1998, at 172.

[43] See WHO Task Force, 1989, at 722, 724 (subjects where RU 486/sulprostone failed weighed 65.7 + or - 10.2 kg; those with complete abortion, 54.7 + or - 8.3 kg; and those with incomplete abortion, 54.5 + or - 10.6 kg). But see Thong & Baird, 1992 (complete abortion rate not influenced by body mass index; however, the study focused on the clinical efficacy of RU 486/misoprostol abortion in only 100 subjects, not on predictors of failed attempted abortion).

[44] WHO, 1991, at 35, 38 (women with vaginal bleeding prior to gemeprost administration had significantly greater weight (56.1 + or - 7.5 kg) and ponderal index (2.14 + or - 0.26) than those who started to bleed after gemeprost (53.7 + or - 7.4 kg; 2.06 + or - 0.23)).

[45] See discussion *infra* Section 4.a.(5) and accompanying footnotes.

[46] One study found a higher rate of failure in patients over the age of 34. Thonneau, et al., Analysis Of 369 Abortions Conducted By Mifepristone (RU 486) Associated With

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not overweight and do not smoke. However, even this population will not be free of substantial adverse experiences, such as:

- heavy bleeding requiring medical intervention (up to 4% of users);47/
- pelvic or abdominal pain (up to 94.1% of users);48/
- infection (5% of users);49/ and
- cardiovascular conditions and accidents (up to 1.2% of users).50/

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Sulprostone In A French Family Planning Center, 61 Fertility & Sterility 627, 628-30 (1994) (hereafter "Thonneau, et al., 1994") ("The patient characteristics that correlated with failure were age over 34 years (6% <35 years versus 14% >34 years; P=0.05) . . . .") ("We are not aware of other studies indicating that age (>35 years) is a risk factor for failure. However, age over 35 has been considered to be a risk factor for morbidity. . . .").

47/ For data on RU 486/oral misoprostol abortion, see Thong & Baird, 1992 (4% of users: 1 woman needed emergency curettage for heavy bleeding due to incomplete abortion; 3 women were given intramuscular ergometrine for heavy bleeding at the time of expulsion of products); Peyron, et al., 1993 (0.4% of patients (2 women) in study 1 had hemorrhage requiring hemostatic curettage, with one patient needing a blood transfusion 9 days after misoprostol when hemoglobin fell from 13.0 g/dl to 6.1 g/dl); McKinley, et al., 1993 (5.5% had a drop in hemoglobin >2 g/dl, but no blood transfusions). For additional data on this complication with RU 486 and other prostaglandins, see Table 8.

48/ See Table 6 for pain data on RU 486/oral misoprostol abortion. For pain data on RU 486 with other prostaglandins, see Table 7.

49/ For infection data on RU 486 with prostaglandins other than misoprostol, see Table 3.

50/ For data on RU 486/oral misoprostol abortion, see Peyron, et al., 1993, at 1511 (6 women (1.2%) had a "substantial but transient decrease in blood pressure (more than 30 mm Hg for the systolic pressure and 15 mm Hg for the diastolic pressure) attributable to a vagal reaction secondary to painful uterine cramps."). For data on RU 486 with other
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Because of the known contraindications, complications and adverse effects of RU 486 with or without a prostaglandin, petitioners believe that, on balance, a proper risk/benefit analysis requires FDA to refuse to approve an NDA for RU 486, absent compelling safety and effectiveness data.

e) Incidence Of Complications May Be Underestimated

There is some statistical information on the number of women who suffer from immediate side effects of RU 486/PG abortion, such as fainting, pain, vomiting and diarrhea.[51] However, published studies to date provide little information on the incidence of secondary complications discovered shortly after drug administration (e.g., infection) or even later (e.g., PID, infertility). This is partly due to study protocol deficiencies that require follow-up only for a very limited time period after the abortion procedure.[52] Data also are unavailable or incomplete because of the number of patients

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prostaglandins, see Ulmann, et al., 1992 (reporting 3 myocardial infarctions (1 fatal) and cases of severe hypotension after sulprostone injection).

51/ FDA should consider that complications with pharmaceutical abortion may result regardless of whether the abortion is complete. See Birth Control Trust, Mifepristone In Practice: Running An Early Medical Abortion Service, 38 (1994) (hereafter "Birth Control Trust, 1994") (an early complication rate of 14% among women who had a medical abortion (RU 486/gemeprost) even though 94% had a complete abortion); A World Health Organization ("WHO") study reported that 2.6% of the women with complete abortions (92.7%) required antibiotics to prevent or cure suspected genitourinary infection during a six week follow-up period. WHO, 1991, at 37. See also, WHO Task Force, 1989, at 722 (1.3% of subjects w/complete abortion (88.8% of subjects) given antibiotic therapy because of clinically suspected endometritis).

52/ The three largest studies only followed patients for approximately one week after PG administration. Ulmann, et al., 1992, at 279 ("approximately one week later. . . the
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who fail to return for follow-up examinations.[53] The lack of, or partially-completed, follow-up visits by patients impedes accurate reporting of latent complications and adverse experiences. Given the above factors, petitioners urge FDA to consider the published incidence of complications for RU 486/PG abortion to be underestimated.

f) Poor Patient Compliance With Procedure And Follow-up

Even with physician monitoring of the RU 486 abortion process, poor patient compliance with the procedure and follow-up program is a serious safety and effectiveness concern. An acceptable level of safety for RU 486 or RU 486/PG abortion is contingent on strict patient compliance, and adherence to an established follow-up program.[54] Lack of an effective means to ensure an adequate level of compliance in the

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final outcome of treatment was evaluated."); Aubeny, RU 486 Combined With PG Analogs In Voluntary Termination Of Pregnancy, 7 Adv. Contraception 339, 341 (1991) ("fourth visit took place on day 8-12 after expulsion."); Wu, et al., 1992, at 204 ("On the [illegible]th day after medication, the woman returned to the clinic for evaluation of the result . . . . If complete abortion could not be confirmed, further follow-up on the 14th day was required."). The remaining studies typically follow patients until the onset of their next menstrual period (one, two and four or six weeks after the RU 486 abortion procedure). See, e.g., UK Multicentre Trial, 1990 and the WHO studies.

53/ See *infra* section 3.f. and accompanying footnotes for statistics on lack of patient compliance.

54/ Rodger, et. al., Induction Of Early Abortion With Mifepristone (RU 486) And Two Different Doses Of Prostaglandin Pessary (Gemeprost), 39 Contraception 497, 501 (1989) (hereafter, "Rodger, et. al., 1989") ("Careful follow-up is essential following treatment to exclude the presence of a continuing pregnancy."); Peyron, et al., warned that "[e]ctopic pregnancy is difficult to detect very early, and its possible occurrence makes a follow-up visit 8 to 15 days after the treatment mandatory . . . ." Peyron, et al., 1993, at 1512; Ulmann, et al., 1992, at 283 (RU 486/PG abortion is an "acceptable alternative to
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treatment population is a serious drawback of medical abortion. Even under the carefully controlled conditions of a clinical trial, patient non-compliance has been a problem. The UK Multicentre Trial, 1990 reported that 9 women were lost to follow-up before investigators could confirm that the abortion was complete; 9.35% failed to return for follow-up two days after administration of the prostaglandin; and 21.77% did not return nine days after receiving the drugs.[55/58/]

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surgical procedures, provided that . . . the protocol recommended by the manufacturer is strictly followed."); Rodger & Baird, Induction Of Therapeutic Abortion In Early Pregnancy With Mifepristone In Combination With Prostaglandin Pessary, Lancet ii: 1415, 1417-1418 (1987) ("The occurrence of incomplete abortion after medical termination of pregnancy . . . makes careful follow-up a necessity.").

55/ UK Multicentre Trial, 1990. A study by Ulmann, et al., indicates a lower, but still significant incidence of noncompliance: (1) 0.3% of women given RU 486 were lost to follow-up prior to PG administration; and (2) 0.8% never received a PG even though they had not aborted. Thus, 1.1% of women who received RU 486 as part of an RU 486/PG protocol did not return and/or refused to take the prostaglandin analog. In addition, 2.6% of the women in the study were lost to follow-up after RU 486/PG administration. Ulmann, et. al., 1992, at 280 (There were other protocol violations reported in this study: 11.6% took PG either before or after the protocol time (36-48 hr. after RU 486 intake); and 13.6% had pregnancies beyond the 7 week protocol cut-off (i.e., more than 49 days amenorrhea calculated from the first day of the last menstrual period)). Id.

58/ See also Grimes, et al., 1990 (2.5% of patients were lost to follow-up after RU 486 administration; study did not include PG); Peyron, et al., 1993 (2.8% of the women in study 1 did not return for follow-up after RU 486/misoprostol administration; and 27.6% of the women in study 2 who had not aborted within 4 hours after 400 ug of misoprostol declined to take an additional 200 ug dose); Henshaw, et al., Comparison Of Medical Abortion With Surgical Vacuum Aspiration: Women's Preferences And Acceptability Of Treatment, 307 BMJ 714 (1993) (4% of patients in a study comparing medical to surgical abortion did not return for follow-up visit 16 days later); Hill, et al., The Efficacy Of Oral Mifepristone (RU 38,486) With A Prostaglandin E1 Analog Vaginal Pessary For The Termination Of Early Pregnancy: Complications And Patient Acceptability, 162 Am. J. Obst. Gyn. 414 (1990) (7%, 15%, and 13% of patients did not attend for follow-up at 7, 14.
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Failure to return and/or receive the prostaglandin analog significantly increases the risks associated with taking an ineffective dose of RU 486 alone.[57] In particular, taking RU 486 without a prostaglandin can be expected to increase the risk that surgical intervention will be necessary or that other complications will arise.[58] Furthermore,

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and 28 days after PG administration, respectively); Thonneau, et al., 1994, at 628-29 ("Sixteen patients (4.3%) did not return for follow-up on day 14, and no data about either efficacy or complications are available for these women."); WHO Task Force, 1993, at 534 ("Two women refused the gemeprost pessary .... Six other women received both mifepristone and gemeprost and attended the follow up visit one week later, but they defaulted from attending further follow up visits and attempts to contact them failed."); Indian Council of Medical Research Task Force On Hormonal Contraception, A Multicentre Clinical Trial With RU 486 Followed By 9-Methylene-PGE2 Vaginal Gel For Termination Of Early Pregnancy: A Dose-Finding Study, 49 Contraception 87, 91, 97 (1994) (4 patients (0.88%) did not come back for the PG gel: 3 for "personal reasons" and 1 was lost to follow-up); Maria & Stampf, Termination Of Early Pregnancy Using Mifepristone In Combination With Prostaglandin Analogs, 149 Acta Obst. Gyn. Scand. Suppl. 31 (1989) (4.9% (13 patients) were lost from study and did not receive the follow-up exam on day 10); Swahn & Bygdeman, Termination Of Early Pregnancy With RU 486 (Mifepristone) In Combination With A Prostaglandin Analogue (Sulprostone), 68 Acta Obst. Gyn. Scand. 293, 294 (1989) (hereafter "Swahn & Bygdeman, 1989") (0.85% (one woman) withdrew from study 24 hours after RU 486 administration -- prior to PG administration -- due to nausea); WHO Task Force, 1989, at 720 (0.4% (one woman) stopped RU 486 and did not receive the PG "for personal reasons unrelated to the treatment ...." And 0.4% (one) was lost to follow-up.); Broome, Using Mifepristone In A Family Planning Clinic, 20 Br. J. Family Planning 11 (1994) (11.2% failed to keep follow up appointment. "This rate has become much worse in the last few months. . . .").

57/ Ulmann, et al., 1992, at 280-81 (reporting that the success rate was significantly lower (88.6% instead of 95.3%) in the absence of PG administration and the incidence of ongoing pregnancy was higher (4.6% as opposed to 1.2% overall)).

58/ Id. at 281. Ulmann reported 4.2% of patients who did not receive the PG required vacuum aspiration or D&C because of incomplete abortion (compared to 2.8% of total
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rhesus negative women who do not return for the prostaglandin and an anti-D immunoglobulin injection are at risk for rhesus isoimmunization and its associated complications in subsequent pregnancies.[59] Untimely PG administration (i.e., a time lapse between administration of RU 486 and the prostaglandin less than 36 hours or greater than 48 hours) also reduces the method's effectiveness.[60] As demonstrated by the UK Multicentre Trial and the Ulmann study, a significant number of women -- even in well-organized health care programs -- are at risk of receiving improper care and may be exposed to additional health hazards because of poor compliance.[61]

Petitioners assert that there is no reason for FDA to expect that the prospects for patient compliance will be any better here in the U.S. than observed overseas. Dr. Suzanne Poppema, owner of a Seattle abortion clinic, is currently participating in the

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patients). Also, 2.6% of the group not receiving PG required a hemostatic surgical procedure (compared to 0.7% of total patients).

59/ The protocol followed in most published studies calls for administration of an anti-D immunoglobulin injection for Rh negative women at the time of PG administration. See Thong, et al., Changes In The Concentration Of Alpha-Fetoprotein And Placental Hormones Following Two Methods Of Medical Abortion In Early Pregnancy, 100 Br. J. Obst. & Gyn. 1111 (1993); Urquhart & Templeton, Reduced Risk Of Isoimmunisation In Medical Abortion, 335 Lancet 914 (1990).

60/ Id. at 280-81. Ulmann reported that the time lapse between RU 486 and PG intake had a significant effect on the complete abortion rate. This rate was highest (95.8%) at 36-48 hours, but dropped to 92.8% at less than 36 hours, and 93.9% at more than 48 hours.

61/ UK Multicentre Trial, 1990; Ulmann, et al., 1992, at 283. See also Wu, et al., 1992, at 209 ("It seems that the treatment regimen when followed carefully plays an important role on the effectiveness of the method.").

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clinical trials of RU 486/misoprostol. With regard to patient follow-up, Dr. Poppema commented that even though U.S. clinics routinely include follow-up visits in the price of an abortion "we're lucky if 30% to 40% of these patients ever return."62/ Without assurance of patient compliance, safe and effective medical abortion cannot be provided.

4. FDA Must Require Clinical Data On Unanswered Safety Concerns

To meet its statutory obligation, FDA must require an RU 486 applicant to submit clinical data that addresses all outstanding safety concerns in all population segments affected by RU 486. The population segments affected by RU 486/PG abortion include the aborting mothers, children born after a failed RU 486/PG abortion as well as any children conceived and born after their mother was exposed to these drugs.

a) Aborting Mothers

A review of published data indicates that the potential adverse effects on the subsequent health of an RU 486 user have not been fully investigated. In particular, for the aborting mother there is a paucity of data in the following areas:63/

62/ "With RU-486, Will More Physicians Provide Abortions?," Amer. Med. News, Apr. 12, 1993, at 3.

63/ There is some published medical literature on RU 486 which medical experts assume is scientifically valid. However, this assumption may not be warranted and therefore FDA should not rely on the published literature without verification of the raw data supporting the publication.

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(1) Abortion/Breast Cancer Link

Significant data evidencing a link between induced abortion and breast cancer have now been gathered from many countries, despite major differences in study populations (e.g., Asian, Caucasian, and African-American women) and study designs. Although the link is not yet universally acknowledged, studies which refute the link are seriously flawed. For example, the studies of Vessey, et al., 1982 in England and Gandra, et al., 1993 in Portugal are confounded by the inclusion of spontaneous abortion data,[64] and a study on induced abortion in Sweden was only able to generate an odds ratio significantly less than 1 by gross omissions.[65] As a result, petitioners suggest that FDA carefully review the design of any studies submitted by an RU 486 NDA applicant that evaluate the abortion/breast cancer link. Petitioners also request that FDA refuse to approve any RU 486 NDA submitted without methodologically sound studies with statistically significant data on the association between abortion and breast cancer.

64/ Vessey, et al., Oral Contraceptive Use And Abortion Before First Term Pregnancy In Relation To Breast Cancer Risk, 45 Br. J. Cancer 327 (1982) (this study is composed almost entirely of women who had a spontaneous abortion, with "only a handful" of patients who had undergone induced abortion.); Gandra, et al., Risk Factors For Breast Cancer: A Case-Control Study, 6 Acta Medica Portuguesa 129 (1993).

65/ Lindefors-Harris, et al., Risk Of Cancer Of The Breast After Legal Abortion During First Trimester: A Swedish Register Study, 299 Br. Med. J. 1430 (1989) (authors achieved a borderline significant negative association only by inexplicably excluding women aborted after age 30, and by comparing aborted women to the general population rather than to a bona fide control group. Since the general population had a 20% higher nulliparity rate than the study population of aborted women (49% versus 41%), the known protective effect of parity could account for the apparent protective effect of abortion.).

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Petitioners believe that this data is critical for a comprehensive risk/benefit evaluation of RU 486.

To date, fifteen other epidemiological studies[66] report data on induced abortion and breast cancer risk. All of them are consistent with increased risk. Seven of these[67] are weakened by the lack of age matching of cases and controls,[68] one each in the former USSR (Dvoirin & Medvedev, 1978), Italy (La Vecchia, et al., 1993) and Denmark (Ewertz & Duffy, 1988), and four in the US (Brinton, et al., 1983; Rosenberg, et al., 1988; Moseson, et al., 1993; Daling, et al., 1994). Nevertheless, only two of these do not report an elevated relative risk ("RR") estimate (La Vecchia, et al., 1993 [RR=0.9]; Moseson, et al., 1993 [RR=1.0]); while two of the seven report elevated risks that do not achieve

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66/ Several studies are published in more than one report.

67/ See Dvoirin & Medvedev, Role of women's reproductive status in the development of breast cancer, Methods And Progress In Breast Cancer Epidemiology Research 53 Tallinn, Estonia (1978) (hereafter "Dvoirin & Medvedev, 1978"); La Vecchia, et al., Long-Term Impact Of Reproductive Factors On Breast Cancer, 58 Int. J. Cancer 215 (1993) (hereafter "La Vecchia, et al., 1993") (This study has appeared in at least four separate reports.); Ewertz & Duffy, Risk Of Breast Cancer In Relation To Reproductive Factors In Denmark, 58 Br. J. Cancer 99 (1988) (hereafter "Ewertz & Duffy, 1988"); Brinton, et al., Reproductive Factors In The Aetiology Of Breast Cancer, 47 Br. J. Cancer 757 (1983) (hereafter "Brinton, et al., 1983"); Rosenberg, et al., Breast Cancer In Relation To The Occurrence And Time Of Induced And Spontaneous Abortion, 127 Am. J. Epidem. 981 (1988) (hereafter "Rosenberg, et al., 1988"); Moseson, et al., The Influence Of Medical Conditions Associated With Hormones On The Risk Of Breast Cancer, 22 Int. J. Epidem. 1000 (1993) (hereafter "Moseson, et al., 1993"); Daling, et al., Risk Of Breast Cancer Among Young Women: Relationship To Induced Abortion, 86 J. Nat'l Cancer Inst. 1584 (1994) (hereafter "Daling, et al., 1994").

68/ Controls are generally younger than the cancer patients so relative risk estimates tend to be underestimated and confidance intervals are wider.

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statistical significance (Brinton, et al., 1983; Rosenberg, et al., 1988[69]). One reports a relative risk of 1.71 without showing the presence or absence of statistical significance (Dvoirin & Medvedev, 1978); and two report significantly elevated risks (Ewertz & Duffy, 1988; Daling, et al., 1994).

The other eight studies[70] do compare breast cancer patients with age-matched controls, one in Sweden and Norway (Adami, et al., 1990), two in Japan (Nishiyama, 1982; Hirohata, et al., 1985), two in France (Le, et al., 1984; Andrieu, et al., 1994) and three in the US (Pike, et al., 1981; Howe, et al., 1989; Laing, et al., 1993). Five of them report significantly elevated overall risks of breast cancer with induced abortion. Only Hirohata, et al., 1985, Adami, et al., 1990, and Andrieu, et al., 1994 do not report a

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69/ This study reports relative risks of 1.2-1.3, despite the fact that the median patient age was 12 years greater than the median control age.

70/ See Adami, et al., Absence Of Association Between Reproductive Variables And The Risk Of Breast Cancer In Young Women In Sweden And Norway, 62 Br. J. Cancer 122 (1990) (hereafter "Adami, et al., 1990"); Nishiyama, The Epidemiology Of Breast Cancer In Tokushima Prefecture, 38 Shikoku Med. J. 333 (1982) (hereafter "Nishiyama, 1982"); Hirohata, et al., Occurrence Of Breast Cancer In Relation To Diet And Reproductive History: A Case-Control Study In Fukuoka, Japan, 69 Natl. Cancer Inst. Monogr. 187 (1985) (hereafter "Hirohata, et al., 1985"); Le, et al., "Oral Contraceptive Use And Breast Or Cervical Cancer: Preliminary Results Of A French Case-Control Study, Hormones And Sexual Factors In Human Cancer Aetiology 139 (Elsevier, Amsterdam 1984) (hereafter "Le, et al., 1984"); Andrieu, et al., Familial Risk Of Breast Cancer And Abortion, 18 Cancer Detection & Prevention 51 (1994) (hereafter "Andrieu, et al., 1994"); Pike, et al., Oral Contraceptive Use And Early Abortion As Risk Factors For Breast Cancer In Young Women, 43 Br. J. Cancer 72 (1981) (hereafter "Pike, et al., 1981"); Howe, et al., Early Abortion And Breast Cancer Risk Among Women Under Age 40, 18 Int. J. Epidem. 300 (1989) (hereafter "Howe, et al., 1989"); Laing, et al., Breast Cancer Risk Factors In African-American Women: The Howard University Tumor Registry Experience, 85 J. Nat'l Med. A. 931 (1993) (hereafter "Laing, et al., 1993").

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significant overall risk (RR=1.5, 0.9, and 1.1 respectively). However, Andrieu, et al., 1994 do report a significant relative risk of 7.1 among women with two or more abortions and a positive family history of breast cancer. This interaction of two risk factors is underscored by the disturbing findings of Daling, et al., 1994, who also report greater risks for aborted women with a positive family history.[71] In particular, these authors report an incalculably high risk elevation for such women who had an induced abortion before age 18.

A weakness in study design shared by all but one of the case-control studies is the reliance on patient recall, rather than on prospective data. A bias towards more truthful reporting of induced abortion history by patients versus controls has been suggested.[72] However, the one case-control study based on prospective, computerized data (by the N.Y. State Dept. of Health; Howe, et al., 1989) reports an overall relative risk of 1.9 for induced abortion, similar to most other studies. These authors also report looking for and finding no evidence of response bias. Daling, et al., 1994 also critically evaluate and

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71/ But see Parazzini, et al., Menstrual And Reproductive Factors And Breast Cancer In Women With Family History Of The Disease, 51 Int. J. Cancer 677 (1992) (a large case-control study in Milan, Italy). In Italy, over three-quarters of legal abortions occur among women who have already had one or more children. See Figa-Talamanca, et al., Epidemiology Of Legal Abortion In Italy, 15 Intl. J. Epidem. 348 (1986). This means that these women are at a lower risk of breast cancer anyway, because of the previous live birth.

72/ Lindefors-Harris, et al., Response Bias In A Case-Control Study: Analysis Utilizing Comparative Data Concerning Legal Abortions From Two Independent Swedish Studies, 134 Am. J. Epidem. 1003 (1991); Lindefors-Harris, et al., Risk Of Cancer Of The Breast After Legal Abortion During First Trimester: A Swedish Register Study, 299 Br. Med. J. 1430 (1989).

discount the response bias hypothesis in their report on Washington State women in the Journal of the National Cancer Institute.

One limitation of most studies on induced abortion and breast cancer risk is the lack of post-menopausal patients who were exposed to induced abortion. However, the recent study of Laing, et al., 1993 reports on a patient population mostly over age 50. It shows an increasing relative risk with increasing age, with the relative risk equal to 4.7 in patients over age 50.

In addition to the substantial body of epidemiological evidence for the link between induced abortion and breast cancer, the biological basis for an increased risk of breast cancer following abortion is well documented.[73] A woman's first full pregnancy causes hormonal changes which permanently alter the structure of her breast. Before a woman's first pregnancy, her breasts consist mostly of connective tissue surrounding a branching network of milk ducts, but with relatively few milk-producing cells. With pregnancy, estrogen and other hormones flood the mother's system causing breast cells to proliferate. The network of milk ducts begins to bud and branch, developing "terminal end buds."

73/ For a general discussion of the biological changes in breast tissue during pregnancy, see Russo, et al., Differentiation Of The Mammary Gland And Susceptibility To Carcinogenesis, 2 Breast Cancer Res. Treat. 5 (1982) (hereafter "Russo, et al., 1982").

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Terminal end buds have been shown to be more susceptible to neoplastic transformation.[74] This effect is attributed to the fact that terminal end buds are composed of actively proliferating epithelium. In animal experiments using the carcinogen DMBA, the highest DMBA-DNA interaction is associated with the structure with the highest proliferative rate. *In vitro* experiments using human breast tissue have corroborated this observation.[75]

Skepticism concerning the biologic mechanism underlying the risk-enhancing effect of induced abortion has come recently from Dr. Lynn Rosenberg. Dr. Rosenberg cites the "inconsistent" nature of the association between spontaneous abortion and breast cancer as reason to doubt the underlying mechanism of early pregnancy interruption.[76] If susceptibility is increased by prevention of the tissue maturation that accompanies a full term pregnancy, induced or spontaneous abortions should have the same risk-enhancing effect. It is true that many studies including the most recent American ones (Laing, et al., 1993; Daling, et al., 1994) have shown no association between spontaneous abortions and breast cancer, as has Rosenberg's own research.[77]

74/ Brooks S.C. & Pauley R.J., Breast Cancer Biology, Encyclopedia Of Human Biology (R. Dulbecco, ed. 1991). A full-term pregnancy protects against breast cancer by bringing breast cells into their specialized forms. These mature cells have almost no vulnerability to cancer. Abortion interrupts this process, leaving terminal end buds (immature cells) suspended in high risk transitional states.

75/ Russo, et al., 1982.

76/ Rosenberg, Induced Abortion And Breast Cancer: More Scientific Data Are Needed, 86 J. Nat'l Cancer Inst. 1569 (1994).

77/ Rosenberg, et al., 1988.

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It is entirely plausible that the earlier studies which did show an association were confounded by the misreporting of induced abortion.[78] Lehrer, et al., 1993 have also found a positive association between breast cancer and spontaneous abortion in women heterozygous for a variant of the estrogen receptor gene.[79]

One hypothesis advanced by Daling, et al., 1994 suggests that spontaneous abortions may occur earlier in gestation than most induced abortions, thereby not conferring increased risk. However, their own data still show significantly elevated risks for women who aborted their pregnancy prior to 8 weeks gestation.

There is substantial evidence to support an alternative hypothesis for the clearly emerging dichotomy between the effects of spontaneous versus induced abortion on subsequent breast cancer risk. That is, the same immune mechanism employed by the body to defend against cancer may also be responsible for many spontaneous abortions (and even for the induction of normal labor at term).[80] Specifically, Dr. M.R. Lentz, et al., in California have shown that soluble tumor necrosis factor (TNF) receptor protein is

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78/ See Soini, Risk Factors Of Breast Cancer In Finland, 6 Intl. J. Epidem. 365 (1977); Hadjimichael, et al., Abortion Before First Livebirth And Risk Of Breast Cancer, 53 Br. J. Cancer 281 (1986).

79/ See Lehrer, et al., An Estrogen Receptor Polymorphism And A History Of Spontaneous Abortion--Correlation In Women With Estrogen Receptor Positive Breast Cancer But Not In Women With Estrogen Receptor Negative Breast Cancer Or In Women Without Cancer, 26 Breast Cancer Res. Treat. 175 (1993).

80/ See Lentz, The Phylogeny Of Oncology, 2 Mol. Biother. 137 (1990).

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elevated both in cancer patients[81] and pregnant women.[82] Removal of this protein fraction through selective plasmapheresis has been used successfully in the treatment of human cancers[83] and in the reliable induction of labor and abortion in animals.[84]

Evidence from human clinical experience of heightened immune responsiveness toward cancer and the fetus in spontaneous abortion is provided by the detailed Canadian study of Clark and Chua, 1989. In their series of 154 patients diagnosed with breast cancer while pregnant, only 20% of patients who delivered at term survived 20 years, while 40% of patients who aborted spontaneously survived 20 years. In stark contrast, all patients who underwent "therapeutic abortion" died of the breast cancer within 11 years.[85]

81/ See Gatanaga, et al., Identification Of TNF-LT Blocking Factor(s) In The Serum And Ultrafiltrates Of Human Cancer Patients, 9 Lymphokine Res. 225 (1990a); Gatanaga, et al., Purification And Characterization Of An Inhibitor (Soluble Tumor Necrosis Factor Receptor) For Tumor Necrosis Factor And Lymphotoxin Obtained From The Serum Ultrafiltrates Of Human Cancer Patients, 87 Proc. Nat'l Acad. Sci. 8781 (1990b).

82/ See Lentz & Saltonstahl, Apheresis Of Low Molecular Weight Protein Fraction And The Onset Of Labor, 5 J. Clin. Apheresis 62 (1990) (hereafter "Lentz & Saltonstahl, 1990").

83/ See Lentz, Continuous Whole Blood Ultrapheresis Procedure In Patients With Metastatic Cancer, 8 J. Biol. Response Modif. 511 (1989).

84/ See Lentz & Saltonstahl, 1990.

85/ See Clark & Chua, Breast Cancer And Pregnancy: The Ultimate Challenge, 1 Clin. Oncol. 11 (1989).

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Thus, while more research is needed to detail the long term effects of interrupted pregnancies vis-a-vis breast cancer risk, it is already clear that spontaneous and induced abortion are different events; and that the latter is associated with an increased risk of subsequent breast cancer. Therefore, petitioners believe that at a minimum, FDA has a statutory obligation to require testing that conclusively answers whether RU 486/PG abortion amplifies susceptibility to breast cancer in laboratory animals, in order to evaluate the risk to women. Moreover, since recent studies, especially the NCI-funded study of Daling, et al., 1994, have suggested a particularly strong link in women with a positive breast cancer family history, there is a critical need for retrospective studies on the interaction of induced abortion and family history as risk factors. Petitioners believe that the applicant should be required to provide adequate data on this point in order for the FDA to complete a comprehensive risk/benefit evaluation for RU 486.

(2) Effects on Compromised Patients

Further data is needed to define the effects of RU 486 use in patients who are adrenal compromised, and in patients with liver or kidney disease. RU 486 interferes with cortisol binding to hypothalamic-pituitary tissue, inhibiting the negative feedback mechanisms, resulting in a compensatory increase in serum levels of cortisol and corticotropin. Simultaneously, RU 486 binds to peripheral cortisol receptors, blocking the effect of circulating cortisol.[86] Thus, there is a potential for an inappropriate

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[86] Spitz & Bardin, Clinical Pharmacology Of RU 486 -- An Antiprogestin And Antiglucocorticoid, 48 Contraception 403 (1993) (hereafter "Spitz & Bardin, 1993"); Weiss, RU 486: The Progesterone Antagonist, 2 Arch. Fam. Med. 63 (1993).

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response to stress in users.[87] However, petitioners are not aware of any studies investigating this potential problem. Also, advocates of RU 486 suggest that the infrequent use of RU 486 is unlikely to result in clinical hypocortisolism, but petitioners are aware of only one clinical study (conducted in healthy human males) that may support this contention.[88]

(3) Optimal Dosage Undetermined

The minimum effective dose of RU 486 in combination with a prostaglandin has still not been determined.[89] There is disagreement in the scientific literature about optimal dosage for RU 486. This issue should be settled prior to approval of any NDA; thus, FDA should require optimal dosage studies.

87/ See, e.g., Healy, Clinical Status Of Antiprogesterone Steroids, 8 Clin. Reprod. & Fertility 277, 284 (1985) ("RU 486-induced blockade of the cortisol receptor may prevent the usual glucocorticoid stress response to anaesthesia and surgery in a patient who needs curettage after RU 486 treatment. This might make anaesthesia complex in such patients.").

88/ See Laue, et al., Effect Of Chronic Treatment With The Glucocorticoid Antagonist RU 486 In Man: Toxicity, Immunological, And Hormonal Aspects, 71 J. Clin. Endocrin. & Metab. 1474 (1990) (hereafter "Laue, et al., 1990") (in study designed to examine immune function, blockade of cortisol receptors with RU 486 in 11 healthy males was associated with marked compensatory elevations of plasma ACTH and cortisol; RU 486 (10 mg/kg/day) was administered twice a day for 7-14 days; however, one subject developed signs and symptoms consistent with adrenal insufficiency).

89/ Brogden, et al., Mifepristone: A Review Of Its Pharmacodynamic And Pharmacokinetic Properties, And Therapeutic Potential, 45 Drugs 384, 405 (1993) (hereafter "Brogden, et al. 1993"); Heikinheimo, Antiprogesterone Steroid RU 486: Pharmacokinetics And Receptor Binding In Humans, 69 Acta Obstet. Gynecol. Scand. 357 (1990).

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A study by Grimes, et al., 1990 indicates that further pharmacokinetic research is needed on the use of RU 486 as an abortifacient in obese women. The Grimes study demonstrated an increased risk of failure of RU 486 as a single-agent abortifacient in women with higher body mass.[20] This indicates that the dose of RU 486 required to induce a complete abortion may change with increasing body mass; or possibly that safety and effectiveness of RU 486 cannot be achieved in the obese population.

(4) Systemic Build-Up from Repeat Usage

Petitioners are unaware of any published studies on the effects of repeat usage of RU 486 alone or in combination with a prostaglandin. RU 486 is fat soluble and has been found in adipose tissue.[21] This raises the issue of whether RU 486 can accumulate and be stored in adipose tissue or other body tissues; and if so, what triggers its release. Researchers have detected unmetabolized RU 486 in plasma up to 10 days after single oral administration of 200 mg.[22] This suggests that RU 486 accumulates in the

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20/ See Grimes, et al., 1990, at 913-14 (reporting that risk of failure of RU 486 as single-agent abortifacient was 2.9 times greater for obese women than for women in the lowest body mass group studied). See also *infra* Section 3.d. and accompanying footnotes.

21/ Spitz & Bardin, 1993, at 409; Heikinheimo, Antiprogesterone Steroid RU 486: Pharmacokinetics And Receptor Binding In Humans, 69 Acta Obstet. Gyn. Scand. 357 (1990).

22/ Lahteenmaki, et al., Pharmacokinetics And Metabolism Of RU 486, 27 J. Steroid Biochem. 859 (1987); see also, Heikinheimo, et al., Pharmacokinetics Of The Antiprogesterone RU 486: No Correlation To Clinical Performance Of RU 486, 123 Acta Endocrinologica 298 (1990).

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tissues.[93] If RU 486 can accumulate in the tissues after a single oral dose, the impact of serial use of the drug must be examined. This is justified since the most recent figures indicate that over 42% of women having abortions in the United States have had 1 or more previous induced abortions.[94]

Furthermore, an account of the RU 486/PG abortion experience by a woman who had two medical abortions within a four-month time period indicates that this issue warrants further investigation. After her second RU 486/PG abortion, this woman suffered from extreme fatigue for almost a month, along with an "extreme amount of bleeding" between administration of RU 486 and the prostaglandin.[95] For this individual, the RU 486/PG abortion experience was much more debilitating the second time. Thus, further data, particularly drug disposition and half-life studies, are needed on the systemic build-up of RU 486 when used more than once in a short period of time. If systemic build-up does occur, RU 486, because of its progesterone-like activity, may have an effect on tissue outside the uterus including the fallopian tubes, vagina, ovaries, breasts, and parts of the central nervous system, such as the hypothalamic-pituitary gland, respiratory center, and perhaps cortical function.

93/ See Avrech, Mifepristone (RU 486) Alone Or In Combination With A Prostaglandin Analogue For Termination Of Early Pregnancy: A Review, 56 Fertility & Sterility 385, 386 (1991).

94/ See CDC, "Abortion Surveillance -- United States, 1990," 42 (SS-6) Morbidity & Mortality Weekly Report 29 (Dec. 17, 1993).

95/ See Birth Control Trust, 1994, at 43.

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(5) Blood Loss in Asian-American Women

Although researchers have been unable to identify the cause, Asian women appear to be affected differently by RU 486 than Caucasian women. In particular, Asian women may be at increased risk of heavy bleeding and its associated complications with medical abortion. A World Health Organization ("WHO") study found a significantly longer duration of bleeding in Chinese women than in non-Chinese women.[96] Another study, performed by Chan, et al., compared blood loss in Chinese women after vacuum aspiration with blood loss after administration of RU 486/gemeprost. The researchers found that Chinese women who aborted using RU 486/gemeprost had a significantly greater degree of blood loss than those who aborted by vacuum aspiration.[97] In contrast, a study involving Caucasian women did not demonstrate a significant difference in median blood loss between subjects undergoing surgical and medical abortions.[98] Based on these results, researchers speculated that "the discrepancy might be due to a racial difference" since "changes in the coagulation system in the Chinese

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96/ WHO, 1991, at 35 (when both study groups [repeated doses and single dose RU 486] were combined, the difference between Chinese and non-Chinese subjects was significant [Chinese women: median -- 12 days bleeding; range -- 3 - 45 days, 95th percentile: 37.6 days, n=115; non-Chinese women: median: 10 days bleeding; range 2 - 54 days, 95th percentile: 23.8 days, n=224; P<0.01]). But see, WHO Task Force, 1993, at 534 (reporting no significant difference between Chinese women and non-Chinese subjects).

97/ Chan, et. al., 1993 (2 women (2.08%) required emergency suction evacuation for heavy bleeding; because of heavy bleeding, researchers concluded that "strict supervision is mandatory" for RU 486/PG abortion).

98/ Id. at 93 (commenting on a study conducted by Rodger & Baird, see Rodger & Baird, 1989).

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women as a result of hormone treatment are different from those in Caucasian women."[99] Chan, et al., also speculated that differences in blood loss might be explained by differences in abortion procedure. Specifically, the use or non-use of syntocinon during vacuum aspiration may have an effect.[100]

Petitioners assert that the above hypotheses must be tested by valid scientific study before FDA considers approval of any RU 486 NDA. Without such data, adequate directions for the use of RU 486 in women of Asian descent cannot be provided in approved labeling. Also, and perhaps most importantly, data that conclusively demonstrate an adverse effect or an increased risk factor with use of RU 486 that is specific to a racial group weighs strongly against approval of RU 486.

(6) Increased Vulnerability to Infection/Disease

The risk of immunosuppression must gain greater attention as RU 486 abortion studies have reported infection following RU 486 administration. If women receiving RU 486 become immunosuppressed (due to RU 486 alone, RU 486 and RU 486-elevated cortisol, or RU 486-elevated cortisol and misoprostol), they will be more susceptible to infections, particularly genitourinary infections:

99/ Id. at 93 (citing Wong, et al., The Effect Of Oral Contraceptives On Coagulation And Fibrinolytic Parameters In The Chinese - A Prospective Study, 48 Thromb. Haemostas. (Stuttgart) 263 (1982)).

100/ Id.

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After administration of a single dose of RU 486, cortisol levels rise and remain significantly elevated for at least 72 hours.101/ Unpublished data also indicates that misoprostol produces an increase in serum cortisol in women.102/ Cortisol, as a type of glucocorticoid, is known to adversely affect the body's defenses against disease and injury.103/ In addition, RU 486 itself may have a negative effect on the immune system. The few studies that have examined this possibility are limited and inconclusive but suggest that further research is necessary.104/

For instance, Van Voorhis, et al., reported that women taking RU 486 in abortifacient doses achieve serum concentrations of RU 486 that act in an

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101/ WHO, 1991, at 37; Spitz & Bardin, 1993, at 411. See also WHO Task Force, 1989, at 721; Swahn & Bygdeman, 1989, at 298; Shoupe, et al., 1986, at 457; Swahn, et al., 1989, at 24.

102/ Herting & Nissen, Overview Of Misoprostol Clinical Experience, 31 Dig. Diseases & Sci. 47S, 51S (Feb. 1986 Suppl.) (hereafter "Herting & Nissen, 1986").

103/ Namely, glucocorticoids reduce fluid movement from the blood to the tissues; decrease the permeability of blood vessels. This limits leukocyte migration to the site of tissue injury and reduces the body's ability to fight invading bacteria. Also research suggests that glucocorticoids affect transport of glucose, amino acids, and RNA in lymphocytes; and down regulate gene transcription within the lymphocyte. They also affect the intracellular ability of neutrophils to destroy ingested microorganisms and affect protein expression in lymphoid tissues and lymphoid function. Schulster, et al., Molecular Endocrinology Of The Steroid Hormones 282 (1976).

104/ Laue, et al., 1990; Van Voorhis, et al., The Effects Of RU 486 On Immune Function And Steroid-Induced Immunosuppression In Vitro, 69 J. Clin. Endocrin. & Metab. 1195 (1989) (hereafter "Van Voorhis, et al., 1989"); Bertagna, et al., Peripheral Antiglucocorticoid Action Of RU 486 In Man, 28 Clin. Endocrin. 537 (1988); Emilie, et al., Inhibition Of In Vitro Immunosuppressive Effects Of Glucocorticosteroids By A Competitive Antagonist RU-486, 8 Immunology Letters 183 (1984).

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immunosuppressant manner, and further augment the suppression of immune function caused by cortisol.[105] The Van Voorhis study indicates that further research, in particular, *in vivo* studies in women and *in vitro* studies on a broad assortment of white blood cell types, should be conducted. This research is needed to clarify the immunosuppressive activity of RU 486 itself and the synergistic effects of cortisol/RU 486. Petitioners urge FDA to consider the potential adverse impact on our growing AIDS population of approving RU 486 without definitive answers in these areas.

Two studies have reported enhanced immunosuppression with misoprostol or a PGE1 analog used in conjunction with immunosuppressant drugs.[106] The Moran, et al., study mentions unpublished data that misoprostol acts to enhance the immunosuppressant activity of steroids.[107] Because RU 486 elevates blood cortisol (a steroid), further investigation into the possibility that cortisol and its

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105/ Van Voorhis, et al., 1989.

106/ Redgrave, et al., An In Vitro Comparison Of The Immunosuppressive Potential Of Synthetic Prostaglandin Analogues, 23 Transplant. Proceed. 346 (1991) (an in vitro study which reported that a PGE1analog enhanced the immunosuppressant effects of cyclosporine); Moran, et al., Prevention Of Acute Graft Rejection By The Prostaglandin E1 Analogue Misoprostol In Renal-Transplant Recipients Treated With Cyclosporine And Prednisone, 322 N. Eng. J. Med. 1183, 1187 (1990) (hereafter "Moran, et al., 1990") (reporting that misoprostol acted in a synergistic manner with two known immunosuppressant drugs -- cyclosporine and prednisone (a glucocorticoid) in an in vivo study of kidney transplant recipients). By itself, misoprostol has not demonstrated any adverse effects on the immune system. See Waymack, et al., Effect Of Prostaglandin E On Immune Function In Normal Healthy Volunteers, 175 Surg. Gyn. & Obstet. 329 (1992); Herting & Nissen, 1986, at 51S; Moran, et al., 1990, at 1187.

107/ Moran, et al., 1990, at 1187

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immunosuppression may be enhanced in the presence of misoprostol is important. Such research should be designed to demonstrate the extent of immunosuppression, the molecular mechanisms involved and the subpopulation of white cells (e.g., monocytes, lymphocytes, eosinophils, etc.) affected.

(7) Interference with Transport of Other Drugs/Hormones

Since the human alpha 1-acid glycoprotein (AAG or orosomucoid) is the main plasma transport protein for basic drugs (e.g., imipramine), acidic drugs (e.g., warfarin), and other ligands (e.g., progesterone), it is imperative to study the interactions of RU 486 and its prime plasma protein transporter--AAG. RU 486 binds strongly to AAG variants.[108/] Petitioners are unaware of any studies that explore competitive binding of RU 486 and other drugs or hormones. This research is required to rule out the possibility that RU 486 may compete with other drugs or hormones for AAG transport, thereby slowing or blocking the transport of these medications or hormones.

(8) Impact on Future Fertility

Although there are anecdotal accounts of a return of fertility in women who have taken RU 486 with, or without a prostaglandin,[109/] petitioners are unaware of any

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108/ Herve, et al., Evidence For Differences In The Binding Of Drugs To The Two Main Genetic Variants Of Human Alpha 1-Acid Glycoprotein, 36 Br. J. clin. Pharmac. 241 (1993); Bree, et al., Comparison Of Drug Binding Capacities Of Three AAG Glycan Variants Of Human Origin, 300 Prog. Clin. Biol. Res. 405 (1989).

109/ See Grimes, et al., 1988, at 1311.

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scientific data on the long-term effects of these drugs on the future child-bearing potential of women.

In light of the foregoing discussion, petitioners urge FDA to reflect on the known risks and the potential emergence of post-approval risks to RU 486 users. Pre-marketing studies and studies supporting foreign approval of RU 486 may not be adequately designed to detect or measure serious adverse effects that are infrequent or latent (like those associated with DES). Petitioners assert that there are sufficient quantifiable safety concerns and unquantifiable potential health risks that warrant requiring further study of the effects of RU 486 on users. In view of the availability of alternative abortion methods, there is no compelling reason for FDA to approve an NDA for RU 486 as an abortifacient, particularly when the known adverse effects and potential health risks to women are taken into consideration.

b) Children Born After Exposure To RU 486 And/Or Misoprostol

Although RU 486 has been used to abort human pregnancies since 1982, there are limited data on the effects of RU 486 or misoprostol on an embryo that is carried to term despite administration of these drugs to the birth mother. For subsequent born children, there are insufficient clinical data in the following areas:

(1) Risk of Congenital Malformation in a Continued Pregnancy

The risk of congenital malformations in children born after a failed RU 486 abortion must be defined further. Since a significant percentage of pregnancies continue

despite the administration of RU 486 or RU 486 with a prostaglandin.110/ the issue of deformities is not theoretical.

Risk Associated with RU 486 -- Research has shown that both mifepristone, and probably its major metabolite, cross the placenta.111/ There is limited and contradictory data on whether the direct action of RU 486 on "the trophoblast/placenta might result in retardation of the embryos and contribute to the birth of children with abnormalities."112/ In animals, two studies have demonstrated teratogenic activity of RU 486. A study by van der Schoot & Baumgarten, involving the neonatal administration of RU 486, resulted in behavioral and anatomical defects in male and female rats.113/ In female rats, development of the reproductive tract was permanently affected. Abnormalities occurred in oviduct and ovarian capsule structure, as well as the

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110/ With RU 486 alone, from 8.3% to 46.3% of pregnancies have continued. See Table 9 for complete statistics. After RU 486/oral misoprostol administration, from 0.45% to 2.5% of pregnancies have continued (see Table 10 for statistics); and after medical abortion with RU 486 and other prostaglandins, from 0.4% to 6.2% of pregnancies have continued (see Table 11 for statistics).

111/ Hill, et al., Transplacental Passage Of Mifepristone And Its Influence On Maternal And Fetal Steroid Concentrations In The Second Trimester Of Pregnancy, 6 Hum. Reprod. 458 (1991) (hereafter "Hill, et al., 1991"); Hill, et al., The Placental Transfer Of Mifepristone (RU 486) During The Second Trimester And Its Influence Upon Maternal And Fetal Steroid Concentrations, 97 Br. J. Obst. Gyn. 406 (1990b) (hereafter "Hill, et al., 1990b"); Frydman, et al., Transplacental Passage Of Mifepristone, ii Lancet 1252 (1985).

112/ Raymond, et al., 1991, at 76-79.

113/ van der Schoot & Baumgarten, Effects Of Treatment Of Male And Female Rats In Infancy With Mifepristone On Reproductive Function In Adulthood, 90 J. Reprod. Fert. 255 (1990).

development of anovulatory polyfollicular ovaries during adulthood. There was interference, after some delay, with normal ovarian cyclicity and reduced fertility (smaller litters). A temporary suppression of adrenal gland growth was noted in both male and female rats. In males, permanently retarded testicular size and growth, delay of puberty and reduced growth around puberty occurred. Male rats also exhibited a reduced capacity to ejaculate. This deficiency in male sexual behavior resulted in relative infertility. Finally, early exposure to RU 486 resulted in the expression of female sexual behavior in adult males.

A study of rabbits reported various anomalies in fetuses that were not aborted following mifepristone administration. These included skull deformities, non-fused eyelids, absence of closure of the vertebral canal, and extremely small size.[114/] On the other hand, no evidence of teratogenicity was found in a limited trial of monkey embryos exposed to RU 486.[115/] Nevertheless, researchers cautioned that "this study and our conclusions are limited by the small numbers of observations, as well as the particular

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114/ Jost, Animal Reproduction -- New Data On The Hormonal Requirement Of The Pregnant Rabbit: Partial Pregnancies And Fetal Abnormalities Resulting From A Treatment With A Hormonal Antagonist Given At Sub-Abortive Dosage, 303 C.R. Acad. Sci. III 281 (1986); Silvestre, et al., Voluntary Interruption Of Pregnancy With Mifepristone (RU 486) And A Prostaglandin Analogue, 322 N. Eng. J. Med. 645 (1990) (hereafter "Silvestre, et al., 1990") (deformities were reportedly "attributed to uterine contractions secondary to decreased progesterone activity.").

115/ Wolf, et al., Tolerance Of Perinidatory Primate Embryos To RU 486 Exposure In Vitro And In Vivo, 41 Contraception 85 (1990) (hereafter "Wolf, et al., 1990"); see also, Raymond, et al., 1991, at 78.

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conditions tested here."116/ "[W]e cannot be assured by the data presented here that exposure to RU 486 is never teratogenic. . . ."117/

In humans, there have also been mixed reports. Dr. Andre' Ulmann, Medical Director, Roussel Uclaf, reported that six children born after failed mifepristone abortions are normal.118/ However, one fetus exposed to RU 486 in early pregnancy had multiple abnormalities, including sirenomelia (fused lower extremities), a cleft palate and lip, micrognathia and hygroma.119/ Although the observations were reported to Roussel Uclaf at the time of occurrence, data necessary for an objective evaluation of these cases, such as follow-up studies on lost-to-view women who have taken mifepristone and other pharmacovigilance data, are still unavailable today.120/

116/ Wolf, et al., 1990, at 90.

117/ Id. Furthermore, one study in mice found that RU 486 retarded embryonic development in vivo and acted directly on the embryo, interfering with its development in vitro. Yang & Wu, RU 486 Interferes With Egg Transport And Retards The In Vivo And In Vitro Development Of Mouse Embryos, 41 Contraception 551 (1990).

118/ Institute of Medicine, 1993, at 28.

119/ See Pons, et al., 1991 (although the researchers couldn't determine whether the abnormalities were related to RU 486, they concluded that "a deleterious effect of mifepristone cannot be ruled out."). For explanation of micrognathia and hygroma see *infra* footnote 21.

120/ See Pons & Papiernik, Mifepristone Teratogenicity, 338 Lancet 1332 (1991). In addition, the published studies on human fetal exposure to RU 486 during the second trimester are inconclusive. Hill, et al., 1991 found no statistically significant changes in fetal concentrations of progesterone, oestradiol or cortisol, but a significant increase in fetal aldosterone occurred 4 and 24 hours after drug intake. However, researchers concluded that "[t]he importance of the increased fetal aldosterone levels is uncertain. In view of the small number of patients in each group this may have occurred by chance and (Footnote continued on next page)

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Risk Associated with Prostaglandins -- Prostaglandins have been reported to cause deformities in both human beings and animals.[121] In particular, misoprostol has been associated with two specific types of anomalies in children. Five cases of a frontal and/or temporal defect in the skull without other anomalies were found in babies born to women who had taken 400-600 ug of misoprostol orally and/or vaginally in the first trimester.[122] Gonzalez, et al., reported seven children with limb abnormalities, four of whom also had a diagnosis of mobius sequence.[123] The mothers all had taken 200-1800 ug of misoprostol orally and/or vaginally between 4 and 12 weeks amenorrhea to attempt abortion.[124] It is still unclear as to whether these deformities were directly caused by misoprostol.[125] Fonseca, et al., concluded that "[a] deleterious effect of misoprostol plus

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similarly because of the study size, any effect of mifepristone on the other parameters studied cannot be totally excluded." Id. at 461. See also Hill, et al., 1990b.

121/ Silvestre, et al., 1990; Raymond, et al., 1991 at 89-90; Schonhofer, Brazil: Misuse Of Misoprostol As An Abortifacient May Induce Malformations, 337 Lancet 1534 (1991); Collins & Mahoney, Hydrocephalus And Abnormal Digits After Failed First-Trimester Prostaglandin Abortion Attempt, 102 J. Pediatrics 620 (1983).

122/ Fonseca, et al., Misoprostol And Congenital Malformations, 338 Lancet 56 (1991); Fonseca, et al., Misoprostol Plus Mifepristone, 338 Lancet 1594 (1991) (hereafter "Fonseca, et al., 1991").

123/ Mobius syndrome is characterized by congenital facial diplegia and a developmental bilateral facial paralysis associated with oculomotor or other neurological disorders. See Stedman's Medical Dictionary 1391 (5th ed. 1982).

124/ Gonzalez, et al., Limb Deficiency With Or Without Mobius Sequence In Seven Brazilian Children Associated With Misoprostol Use In The First Trimester Of Pregnancy, 47 Am. J. Med. Genetics 59 (1993) (hereafter "Gonzalez, et al., 1993").

mifepristone on the development of the fetus cannot be ruled out. Firm evidence on freedom from congenital malformations is needed before this drug [misoprostol] can be promoted for use in pregnancy termination."126/ Therefore, petitioners assert that additional data must be collected to quantify the risk of congenital malformations in children born after failed RU 486 abortion with or without a prostaglandin.

(2) Risk of Congenital Malformation in Future Generations

RU 486 and two of its major metabolites cross the blood-follicle barrier of human pre-ovulatory follicles. Cekan, et al., found high concentrations of RU 486 and its metabolites in the follicular fluid.127/ This raises serious questions on the effect of

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125/ Many children exposed to misoprostol in utero appear normal. Schuler, et al., obtained information on 17 babies born to women who took misoprostol as an abortifacient during the first trimester and did not abort. No major malformations were found, although one child had a preauricular tag. Schuler, et al., Teratogenicity Of Misoprostol, 339 Lancet 437 (1992). "However, . . . we cannot evaluate the exposure risk since we do not know the drug effect in embryos (or fetuses) that are aborted." Gonzalez, et al., 1993, at 64.

126/ Funseca, et al., 1994.

127/ Cekan, et al., Levels Of The Antiprogestin RU 486 And Its Metabolites In Human Blood And Follicular Fluid Following Oral Administration Of A Single Dose, 4 Hum. Reprod. 131 (1989) (researchers note that "the morphological appearance and cleavage rate of the oocytes fertilized in vitro were not affected by the treatment with RU 486"). However, the fertilized eggs were only developed to the four- to eight-cell stage. And "the developmental capacity of the oocytes after fertilization in vitro could not be fully determined, since the cleaving embryos were not replaced in a recipient uterus." See Raymond, et al., 1991, at 75 (citing Messinis & Templeton, The Effect Of The Antiprogestin Mifepristone (RU 486) On Maturation And In-Vitro Fertilization Of Human Oocytes, 95 Br. J. Obst. & Gyn. 592 (1988) (hereafter "Messinis & Templeton,
(Footnote continued on next page)

RU 486 on the thousands of immature eggs in the ovaries of a woman that has been exposed to the drug.

(3) Risk of Premature Delivery in Continued Pregnancies

Furthermore, data must be collected to assess the risk of premature delivery in a continued pregnancy due to the softening and dilation of the cervix caused by RU 486.[128/] Petitioners are unaware of any such published data.

(4) Related Risks

A study conducted by Wiedemann, et al., raises questions about the potential effects of RU 486 (and its metabolites) on fetal brain development, in utero fetal sleep patterns and fetal cortical development.[129/] Petitioners are unaware of any studies conducted on the foregoing effects, or on the effect of fetal exposure to RU 486 on an infant's normal postpartum sleep patterns.

In addition, petitioners are unaware of any published studies on the potential carcinogenic, teratogenic, reproductive or behavioral post-birth effects of fetal exposure to RU 486 and its metabolites. Given the tragic experience with diethylstilbestrol (DES), these potential risks to subsequent born children exposed to RU 486 in utero should be

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1988")). Interestingly, the women who received RU 486 had fewer eggs which fertilized in vitro as compared to the controls, although the difference was not statistically significant. Messinis & Templeton, 1988, at 593.

128/ Spitz & Bardin, 1993, at 417; Grimes, 1993, at 173.

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quantified by clinical data. Also, the possible adverse effect on fetal development of a rise in fetal cortisol levels induced by RU 486 should be studied.130/

Petitioners believe that there exists adequate concern for the safety of subsequent born children to postpone the approval of RU 486 pending: (1) the development and implementation of a voluntary RU 486 pregnancy registry, and (2) the generation of data on the potential mutagenic, carcinogenic, and reproductive effects of RU 486 on children born to women that received RU 486 during their pregnancy.

5. If Approved, Safety Mandates Labeling Limits

Notwithstanding the above discussion, should the Commissioner find that an NDA for RU 486 as an abortifacient meets all statutory and regulatory requirements, petitioners request that the Commissioner place stringent limitations on the terms and conditions for use of the drug. To accomplish this objective, the agency should require that: (1) the labeling of the drug bear the limitations and conditions set forth below; and (2) the drug be accompanied by patient brochures to assist patients in making well-informed medical decisions.

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129/ Wiedemann, et al., in a limited study, examined the role of glucocorticoids in sleep and demonstrated that RU 486 as a glucocorticoid receptor blocker disrupts sleep patterns. See Wiedemann, et al., Antiglucocorticoid Treatment Disrupts Endocrine Cycle And Nocturnal Sleep Pattern, 241 Eur. Arch. Psych. Clin. Neurosci. 372 (1992).

130/ Hill, et al., 1991 reported "a trend to higher . . . fetal cortisol concentrations 24 and 48 h after treatment, [however,] this increase failed to reach statistical significance. . . ." Id. at 460-61.

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a) Indications And Usage

In order to minimize adverse health risks, the following information must be included in the labeling for RU 486:

(1) Approved only for use by physicians in ambulatory care facilities or hospitals that meet the standards of the Joint Commission on Accreditation of Healthcare Organizations.

(2) Approved only for use as an abortifacient in conjunction with prostaglandin analogs.

(3) Approved only for termination of pregnancies documented by ultrasound to be intrauterine and within 49 days amenorrhea.

Based on a review and medical expert evaluation of published scientific literature, petitioners believe that ambulatory care facilities or hospitals that meet the standards of the Joint Commission on Accreditation of Healthcare Organizations are required to control the risks of RU 486/PG abortion. This procedure requires the available surgical staff, resuscitation equipment, and adequate blood stores that only an accredited ambulatory care facility or hospital can provide.131/

Further, although petitioners believe that the RU 486 abortion procedure cannot reach a controllable level of safety regardless of the approved conditions for its use, petitioners request that in the event that RU 486 is approved as an abortifacient, it be approved only for use in conjunction with prostaglandin analogs. RU 486 used in

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131/ See additional discussion *infra* Section 6.

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combination with a prostaglandin analog achieves a far more acceptable level of safety and effectiveness, than as a single agent.

Furthermore, the RU 486 abortion regimen requires precise gestational dating to minimize the risk of incomplete abortion and excessive bleeding. Effectiveness of RU 486/oral misoprostol decreases from approximately 96% within 49 days amenorrhea to only 89% within 50-63 days amenorrhea.[132] Also, the amount of blood loss increases significantly with advancing gestation.[133] A sonogram provides the most accurate measure of gestational age presently available.[134] Requiring vaginal ultrasonography or a pelvic ultrasound scan as part of the procedure is essential in order to avoid the risks associated with RU 486/oral misoprostol after 49 days amenorrhea.

132/ See Table 4.

133/ Rodger & Baird, 1989, at 445 ("It is likely that as pregnancy advances and the fetus and placenta increases in size, there is a larger vascular area from which bleeding can occur.").

134/ According to D. Danforth & J. Scott, there are several methods used to determine gestational age. Because of the unreliability of alternative methods, sonography is recommended as a standard abortion practice for assessing gestational age. Alternative methods include: (1) patient's menstrual history (least reliable method -- predictive only to within a margin of 3 weeks with 90% confidence, even if date of last menstrual period is known with certainty); (2) pelvic examination (inaccurate to plus/minus 2 weeks; with retroverted uterus (30% of women) inaccuracy reaches plus/minus 4 weeks); (3) maternal perception of fetal movement (only useful as "rough estimate"); and (4) measurement of fundal height (useful only to corroborate other clinical estimations of gestational age). Danforth & Scott, Obstetrics & Gynecology 263, 365-66 (5th ed. 1986); Hern, Abortion Practice 69-70, 109, 207 (1984) (sonography "appears to be considerably more accurate . . . than are menstrual dates and even a careful examination by an experienced physician." Any doubt concerning length of gestation should be checked by real-time ultrasound examination.).

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A sonogram also provides an effective means of confirming that the pregnancy is intrauterine prior to administering RU 486. Women with ectopic pregnancy should not receive RU 486. The drug is believed to act primarily at the endometrium and myometrium, making the drug ineffective for extrauterine pregnancy.[135/] An untreated ectopic pregnancy puts a woman at continued risk of serious complications, such as severe extrauterine hemorrhage.[136/] Requiring a sonogram reduces the risk of the drug being used inappropriately in a patient with ectopic pregnancy.

b) Contraindications

The subpopulation of potential RU 486 users for whom the safety of RU 486/PG abortion cannot reach a controllable level is extensive. If RU 486 is approved, petitioners believe that the following contraindications must be noted in the labeling for the drug.

(1) Contraindicated for termination of pregnancy greater than 49 days amenorrhea.

(2) Contraindicated for termination of pregnancy in women with asthma, adrenal insufficiency, cardiovascular disease, coagulation or clotting disorders or women receiving anticoagulants.

135/ Rodger, et al., 1989, at 501 ("It is important that an intrauterine pregnancy be established prior to treatment as mifepristone seems ineffective in the disruption of ectopic pregnancy."); Weiss, RU 486: The Progesterone Antagonist, 2 Arch. Fam. Med. 63, 66 (1993); Levin, et al., Mifepristone (RU 486) Failure In An Ovarian Heterotopic Pregnancy, 163 Am. J. Obst. Gyn. 543 (1990); Baulieu, Contragestion And Other Clinical Applications Of RU 486, An Antiprogesterone At The Receptor, 245 Science 1351 (1989).

136/ WHO Task Force, 1993 (1 patient in the study had undiagnosed tubal pregnancy which ruptured 2 weeks after an RU 486/PG abortion).

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(3) Contraindicated for women under age 18 years.137/ Not recommended for women over age 35 years.

(4) Contraindicated in pregnancies in women with recent unhealed Caesarean section.

(5) Ectopic Pregnancy -- RU 486 should not be used if ectopic pregnancy is suspected. Vaginal ultrasonography or pelvic ultrasound scan is required to confirm intrauterine pregnancy prior to RU 486 administration. Use in ectopic pregnancy may result in severe extrauterine hemorrhage.

c) Warnings

(1) Clotting Disorders/Anticoagulants -- RU 486 may induce considerable uterine blood loss in women with a clotting disorder or receiving anticoagulant drugs such as sodium warfarin (Coumadin). Women with clotting disorders should not receive RU 486.

(2) Cardiovascular Reactions -- Serious cardiovascular events have occurred with the RU 486/sulprostone abortion method (3 myocardial infarctions (1 fatal), 3 cases of severe hypotension). One patient death has been reported with misoprostol, in addition to clinically significant hypotension. Myocardial infarction has not been reported as a complication of RU 486/vaginal gemeprost. RU 486 plus any prostaglandin should not be used in women who smoke heavily, women over 35, or women who have any other increased risk of cardiovascular events.

(3) Any infection within the female reproductive tract should be treated prior to abortion. Failure to do so could result in a life-threatening bloodstream infection from the

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137/ Petitioners are unaware of any studies demonstrating safety and/or effectiveness of RU 486 in the pediatric population.

induction of uterine contractions and bleeding during medical abortion.

(4) Uterine tumors and endometriosis, if severe, could produce increased bleeding, retained pregnancy products, and possibly intraperitoneal bleeding.

(5) Acetaminophen may enhance pain during medical abortion and should be avoided. Drugs that affect prostaglandin synthesis, such as aspirin and nonsteroidal anti-inflammatory drugs, may affect the efficacy of RU 486/PG abortion and should be avoided until follow-up.

(6) Induction of abortion is associated with an increased risk of developing breast cancer later in life. This risk is even higher in women with first or second degree family history (sister, mother, grandmother, or aunt) of breast cancer.

d) Precautions

Based on a review of the medical literature and medical evaluation, petitioners believe that in order to ensure a controlled level of safety and effectiveness for RU 486 administration, the following information for prescribing physicians should be included in the product's labeling. In addition, petitioners believe that the following patient information must be provided in patient brochures to enable pregnant women considering abortion to make informed medical decisions.

(1) Information for Physicians

- RU 486 should be used with caution in women with epilepsy, intestinal disease, hematological disorders, women who are anemic, immune compromised, or have liver or kidney disease.