The Breast Cancer Center at Long Beach Memorial Center in Long Beach, California is currently conducting a trial on this use with mifepristone.

Endometriosis

Endometriosis is a disease that results in the lining of the uterus (the endometrium) being found outside the uterus. This tissue reacts to the normal hormonal fluctuations in the menstrual cycle, sometimes forming scar tissue and causing severe pain. There is no known cure for this condition. In very limited studies, mifepristone reduces pelvic pain associated with endometriosis, but it has not been shown to treat or lessen the condition itself.

An incomplete trial at the University of California at San Diego took place to study mifepristone's effect on endometriosis. It is uncertain whether this trial will resume.

Brain Tumor Research (Benign Meningioma)

Meningiomas are slow-growing tumors found in membranes surrounding the brain, and are most times considered inoperable. These growths have many progesterone receptors. Like breast cancer, further research must be conducted to determine mifepristone's efficacy in treating this condition. One trial of 14 patients with inoperable meningiomas showed objective response in five patients and subjective response in three patients. Another study for this use is underway through a network of US universities, research centers, and the National Cancer Institute.

Sources:

Bryant M. RU 486 and Related Drugs May Bring Far-Reaching Benefits. National Research Council *NewsReport.* (The Research Council is jointly administered by the National Academy of Sciences, National Academy of Engineering, and the Institute of Medicine.) Fall 1993.

Spitz IM, Bardin CW. Mifepristone (RU 486) - Modulator of Progestin and Glucocorticoid Action. *New England Journal of Medicine.* August 5, 1993.

Current Research on the Reproductive Uses of Mifepristone. *Outlook.* Program for Appropriate Technology in Health (PATH). April 1994.

APPEARS THIS WAY
ON ORIGINAL

(STILL SUBJECT TO CHANGE)

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HOLD FOR RELEASE
27 October 1994

The Population Council Announces Mifepristone (RU 486) Clinical Trials Are Under Way in the U.S.

NEW YORK--The Population Council announced today (27 October 1994) that the U.S. clinical trials of mifepristone (RU 486) for use in medical abortion are under way at over a dozen clinics around the country. The trials will involve 2100 women volunteers over the age of 18 who are in the early weeks of pregnancy. Enrollment of women volunteers has already started.

The purpose of these trials is to determine the safety, efficacy, acceptability, and feasibility of using mifepristone plus a prostaglandin to induce abortion in women with up to 63 days of amenorrhea and to gather data for registration of the drug with the US Food and Drug Administration. Mifepristone in combination with a prostaglandin is approved for use in medical abortion in France, the United Kingdom, and Sweden.

In a statement, Mrs. Margaret Catley-Carlson, President of the Population Council, described mifepristone as an "important scientific advance in women's reproductive health care," shown in numerous studies to be safe and effective for early medical abortion. "Over 150,000 women have used the drug safely in Europe; over 52,000 French women have used the same combination of mifepristone and prostaglandin that is being used in the U.S. We believe this will provide an equally safe alternative to surgical abortion that women can use in the earliest weeks of a pregnancy. Women who have used this regimen report it is similar to a natural miscarriage."

Mrs. Catley-Carlson predicted that medical abortion "eventually will increase women's access to abortion services and make them more private. Women will be able to obtain medical abortion at doctor's offices, free of anti-choice violence and harassment. We believe mifepristone will not lead to an increased number of abortions--it has not done so in France, where it has been available since 1989--but it will expand women's options."

At the recent population conference in Cairo, Mrs. Catley-Carlson said, "the international community strongly affirmed that unsafe abortion is a major public health concern and that unwanted pregnancies should be prevented through expanded and improved family planning

services. This is the Population Council's position as well. We are an international, nonprofit, research organization. We are not abortion advocates; we promote the use of contraception. We have three interests: prevention of unwanted pregnancy through development of safe, effective contraceptives; prevention of unsafe abortion, which is responsible for thousands of maternal deaths and illnesses, particularly in developing countries; and--because abortion exists and is legal-- development of alternative safe methods of abortion."

In May 1994, Roussel Uclaf, developer of mifepristone, announced it had donated the U.S. rights to the drug, without remuneration, to the Population Council. The Council thus became the organization to conduct clinical trials in the U.S., select a manufacturer and a distributor, and file the New Drug Application with the FDA.

Clinic Selection

In selecting the clinics, the Population Council looked for institutions experienced in providing high quality abortion services, with scientific investigators of excellent clinical capability and the ability to work under scientific study conditions. Each potential clinic was inspected by Council monitors. Participating sites are hospital-based clinics, Planned Parenthood and Feminist Health Center facilities, and free-standing abortion clinics. The sites are geographically spread and have diverse clientele.

The Council said it would not identify the participating sites to protect clinic security and the confidentiality of the women who volunteer for these trials. However, individual clinics and women may choose to identify themselves and discuss their experiences. Women seeking medical abortion will find out about availability through a variety of means: some clinics may advertise the trial; some may announce to the media that they are trial sites; health care providers in other facilities may make referrals; some women will hear about it from friends. The Population Council will not refer patients to individual clinics.

Two-Drug Regimen

The procedure involves two drugs, taken two days apart. On the first day, following medical examination, counseling, and signing of informed consent documents, the patient swallows three tablets of mifepristone. She returns two days later for two tablets of misoprostol, a prostaglandin, and remains in the clinic for four hours. by the end of this period, about 70 percent of the women have a medical miscarriage. The other women will abort after they leave

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the clinic. The woman returns for a third visit two weeks after taking the mifepristone, to ensure that the treatment has been effective. The mifepristone/oral prostaglandin combination fails in about four of every 100 cases. Failures include both ongoing pregnancies (1 in 100) and incomplete abortions (3 in 100). If the medical regimen fails, the abortion should be completed surgically, by vacuum aspiration or curettage.

Side effects, which occur primarily after taking the oral prostaglandin, can include cramps and abdominal pain similar to those associated with a very heavy menstrual period; nausea, vomiting, and diarrhea, sometimes requiring medication; and/or uterine bleeding similar to a heavy period and lasting at least one week. Uterine bleeding and spotting that is not heavy can last for one to three weeks. In rare cases, if uterine bleeding is extremely heavy, the woman may require surgical abortion and/or blood transfusion.

Successful medical abortion avoids a surgical procedure. There are no risks of anesthesia or uterine perforation or cervical canal injury, rare complications of surgical termination of pregnancy. The mifepristone/misoprostol combination can be used in the earliest weeks following conception.

Mifepristone is an antiprogestin. One of its actions is to interrupt pregnancy in its early stages by blocking the action of the natural hormone, progesterone, which prepares the lining of the uterus for a fertilized egg and then maintains the pregnancy. Without the effect of progesterone, the lining of the uterus softens and breaks down, expelling any fertilized egg through menstruation. Prostaglandins are substances made naturally by the lining of the uterus. The prostaglandin in this treatment works by causing contractions of the uterus, expelling a fertilized egg.

# # #

The Population Council, a nonprofit, nongovernmental research organization established in 1952, has a multinational Board of Trustees; its New York headquarters supports a global network of regional and country offices. The Council seeks to improve the wellbeing and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council ·analyzes population issues and trends; ·conducts biomedical research to develop new contraceptives; ·works with public and private agencies to improve the quality and outreach of family planning and reproductive health services; ·helps governments to influence demographic behavior; ·communicates the results of research in the population field to appropriate audiences; and ·helps build research capacities in developing countries.

The Population Council

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Mifepristone and Prostaglandin
CLINICAL TRIALS

General information about medical abortion and the clinical trials

What is the purpose of the clinical trials?
The purpose of these trials is to determine the safety, efficacy, acceptability, and feasibility of mifepristone plus prostaglandin in inducing abortion, when administered to women with amenorrhea up to 63 days. In France the mifepristone/prostaglandin combination is used to terminate pregnancies in women with amenorrhea of 49 days or less, but in the United Kingdom and Sweden, the combination is used in women with amenorrhea up to 63 days. The trials will reinforce the French data and subsequent experience and perhaps extend the window of effectiveness from 49 to 63 days of amenorrhea.

How does mifepristone work?
Mifepristone is an antiprogestin. One of its actions is to interrupt pregnancy in its early stages. It does this by blocking the action of the natural hormone, progesterone, which prepares the lining of the uterus for a fertilized egg and then maintains the pregnancy. Without the effect of progesterone, the lining of the uterus softens, breaks down, and menstruation begins. Any fertilized egg is expelled through menstruation. Prostaglandins are natural substances made by the lining of the womb during menstruation. The prostaglandin works by causing contractions of the uterus, expelling a fertilized egg.

Where has mifepristone been used?
Since 1981, women in 20 countries (including the United States) have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. All the studies have shown mifepristone to be safe and effective. Government regulatory agencies in France, Great Britain, China, and Sweden approved the drug for marketing, following clinical studies like the one being conducted in the United States. In Europe, over 150,000 women have used mifepristone as a medical abortifacient in combination with various prostaglandins: injectable, vaginal suppository, or oral.

How many women have used the mifepristone/oral prostaglandin combination?
In Europe, there is now an accumulated experience with over 52,000 women who have received mifepristone followed 48 hours later by the oral prostaglandin, misoprostol, at the dose to be used in the U.S. trials. A study published in the *New England Journal of Medicine* in May 1993 showed the combination of mifepristone and oral prostaglandin to be effective "for the termination of early pregnancy in terms of success, tolerance, safety, and practicality." The small dosage of oral prostaglandin taken following use of mifepristone is less than the dosage taken every day by those who use the medication for ulcers.

Do all countries use the same prostaglandin?
No. French women have used mifepristone and an oral prostaglandin since May 1992. The French program originally used both injectable and suppository prostaglandins. English and Swedish women currently use a suppository form of prostaglandin.

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Why combine mifepristone with another drug?
Studies have shown that, by itself, mifepristone is effective 65 to 80 percent of the time, depending on how early it is taken in a pregnancy. When used with a small dose of prostaglandin, the combination is effective in approximately 95 percent of women.

What is the French experience with medical abortion?
France has the most extensive experience with the mifepristone/prostaglandin combination. Mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion. About 70 percent of eligible women--those with less than 49 days of amenorrhea--have selected medical abortion over surgical abortion. Overall, this means that 30 percent of all abortions in France are medical abortions. There has been no increase in the total number of abortions in France since the method was introduced in 1989.

A few studies have been undertaken to determine women's attitudes. The vast majority of women who have chosen this method have been satisfied. In one study of 174 French women, 94 percent said they were satisfied with this form of abortion. They liked the fact that there was no surgery or anesthesia, that the method is non-invasive, that it takes place earlier in a pregnancy than a surgical abortion, and is more "natural." It also puts the abortion procedure more in the hands of the women than the doctor. Not every woman will prefer medical abortion. Some women prefer the surgical method because it is over quickly.

Has the regimen caused any deaths?
There have been no serious heart conditions in the 52,000 women using the mifepristone/oral prostaglandin combination of drugs for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack, occurred during medical abortion following injection of a prostaglandin. These complications have been most often associated with patients who were heavy smokers. There is no evidence that the oral prostaglandin--a different class of prostaglandin widely prescribed for long-term use in the prevention and treatment of peptic ulcer disease--is associated with any such cardiovascular side effects.

Beginning in May 1992 France replaced the injection with the oral prostaglandin. There have been no complications or deaths since. Women who are over 35 and are heavy smokers are not good candidates for the mifepristone/oral prostaglandin regimen.

Are there any long-term health effects from this combined regimen?
In 10 years of clinical use, there is little evidence of risk with mifepristone. It is believed such a risk is unlikely because the drug causes very few side effects; exposure is so brief; the dosage is small; and most of the drug is eliminated from the body within two or three days. The oral prostaglandin has been used safely for gastric ulcers for many years. The dosage taken in conjunction with mifepristone for medical abortion is low.

What is the effect of mifepristone on a woman's future fertility?
There are no indications that use of mifepristone to end a pregnancy has affected a woman's ability to have a baby when she was ready. Women who have taken mifepristone have been able to conceive and subsequently bear healthy children. Having an early medical or surgical abortion has not been proven to make future miscarriage more likely.

Does mifepristone cause fetal deformities?
There is no evidence that it does. But little is known about the effect of mifepristone or prostaglandin on a developing embryo or fetus. Therefore, women ought to have surgical abortions when a medical abortion fails. Only a few instances are known where women decided to continue with their pregnancies after taking mifepristone to produce an abortion. In all but one case, a normal baby was delivered. In that case, a sonogram in the second trimester indicated fetal abnormalities and the woman underwent a surgical abortion. It was not known whether the abnormalities were related to mifepristone. While concern over fetal abnormalities is valid, one should also remember that 6 percent of all newborns have developmental congenital abnormalities, half of them serious.

Why is mifepristone effective only in the earliest weeks of pregnancy?
In the first few weeks following fertilization and implantation, the ovaries produce progesterone. By the ninth and tenth week, the placenta produces progesterone in larger amounts, so that antiprogestins are unable to compete with the natural hormone.

What happens if the drugs fail to end a pregnancy?
The mifepristone/oral prostaglandin combination fails in about four of every 100 cases. Failures include both ongoing pregnancies (1 in 100) and incomplete abortions (3 in 100). When that happens, the abortion should be completed through surgical means, generally vacuum aspiration or curettage. Women in the clinical trial will consent in advance to surgical abortion in case medical abortion fails.

Can a woman change her mind after taking the first drug, and before taking the second?
Good counseling will make sure a woman know that she may risk harming her fetus if she continues her pregnancy after taking mifepristone. But that is her decision. Although the informed consent makes it clear to women that they should not continue their pregnancies after taking mifepristone, no one can or will force a woman to have an abortion.

Why would a woman choose medical abortion instead of surgical abortion?
A woman might choose medical abortion over surgical abortion because:

- It can be used in the earliest weeks following fertilization
- It requires no invasive procedure or surgery
- It requires no anesthesia
- Side effects tend to be moderate
- It does not carry risk of uterine perforation or injury to the cervix
- It has the potential for greater privacy
- Some women feel they have greater control over their own bodies when they use the medical abortion procedure

Why would a woman choose surgical abortion over medical abortion?
A woman might choose surgical abortion over medical abortion because:

- It requires fewer office visits and is over quickly
- It is slightly more effective than medical abortion, where four of every 100 women require surgical abortion
- The woman notices less blood loss and is unaware of the passing of the product of conception

Why might a woman want an early abortion?
A woman can choose medical abortion as soon as she suspects she is pregnant and the pregnancy can be confirmed. If she waited for a surgical abortion, she would have to wait several weeks longer.

Why would a woman choose a method that is not as effective as surgical abortion?
Medical abortion is not as effective as surgical abortion. Women are told that they run the risk of an incomplete abortion--this happens with natural miscarriages--or even an ongoing pregnancy. Despite this, many women choose medical abortion because they feel more in control, because it takes place early in a pregnancy, because it's similar to a natural miscarriage and they do not have to undergo surgery.

Will availability of mifepristone make having an abortion too easy?
Decisions about having an abortion are never easy. Medical abortion is not an easy method. Although it involves taking pills, and no surgery, it is a slower procedure, more like a natural miscarriage.

What is the protocol for the trials?
If the pregnancy has been confirmed, and the woman has not had menstrual bleeding for up to 63 days, she may be eligible to participate in these trials. The regimen requires at least three visits: The first encompasses counseling on available options; full obstetrical and medical history; physical examination; and determination of length of pregnancy via vaginal ultrasound. If there are no contraindications to mifepristone use, the woman will swallow three tablets, each 200 mg, and remain under observation for 1/2 hour. The second visit involves a return to the clinic 36 to 48 hours later; the woman will ingest two 200 microgram tablets of oral prostaglandin under supervision, and remain at the clinic for four hours under the observation of clinic staff. About two-thirds of women abort during this four-hour period. Uterine bleeding will continue for several days, possibly for 4-16 days. The third, follow-up, visit takes place 12 days later (14 days after taking mifepristone), to ensure the abortion is complete. If the clinician is not sure whether abortion has been complete, blood tests or ultrasound will be taken. If abortion is not complete at this time, vacuum curettage will be performed.

What are the side effects from mifepristone and oral prostaglandin use?
Some women do not experience any physical discomfort after taking mifepristone; others have light uterine bleeding in the two days before taking the prostaglandin. The side effects of mifepristone appear to be similar to the side effects of "morning sickness" of a normal pregnancy -- nausea, headache, weakness, and fatigue.

Side effects are more common after taking the oral prostaglandin. They include:

- Cramps and abdominal pain, similar to those associated with a very heavy menstrual period. They are a normal, expected part of the abortion process; some 80 percent of women get them.
- Nausea, vomiting, and diarrhea, sometimes requiring medication
- Uterine bleeding: similar to a heavy period and lasting at least one week, or bleeding and spotting that is not heavy but can last for one to three weeks. In rare cases, if uterine bleeding is extremely heavy, the woman may require surgical abortion and/or blood transfusion.

What is the risk of hemorrhage requiring blood transfusion?
Heavy uterine bleeding can occur, but is rare. Severe hemorrhage sometimes necessitates a blood transfusion. In France, about one in 1,000 women require a transfusion.

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How do you determine the age of a pregnancy?
All pregnancies are dated from the first day of the woman's last menstrual period (LMP). This is known as the duration of amenorrhea. However, those concerned with the actual age of the embryo should realize that there are usually two weeks between the time a woman's menstrual period starts to the time she ovulates. Therefore, 49 days LMP means a 35-day-old embryo, and 63 days LMP means a 49-day-old embryo.

How many women will be taking part in these trials?
Up to 2100 women will volunteer for these trials, at locations around the country.

How will patients be selected for the clinical trials?
Women seeking abortions will go to available providers; at some locations women will be told, "Today you have a choice." Counseling, physical exams, and determination of the age of gestation will be similar to surgical abortion.

How will women find out where the method is available?
Women seeking medical abortion will find out about availability through a variety of means: some clinics may advertise; some may announce they are trial sites or be quoted in news stories. Health care providers in other facilities may make referrals. Some women will hear about it from friends. The Population Council will not refer patients to individual clinics.

Why would women want to participate in this experiment?
Clinical trials like these are required for all FDA approvals. Women who volunteer to participate in these trials are carefully screened and are given sensitive and accurate counseling. In addition, the volunteers know they are participating in a study that will help make this drug available to other American women. Besides, this is not an untested drug. Over 150,000 women have used this drug in Europe, and over 52,000 of them have used the same combination of drugs that is used in the U.S.

Will teenagers be eligible for mifepristone?
Only women 18 and older will be able to participate in the trials.

How much will it cost to take part in the trials?
Women who volunteer to take part in a clinical trial of an experimental drug do not have to pay for it. Neither are they paid to participate.

After mifepristone is approved for marketing, who will be able to provide it?
The mifepristone regimen will be able to be provided by any physician qualified to determine the age of a pregnancy and diagnose the possibility of an ectopic pregnancy. The physician also must be trained and licensed to perform abortions, and have access to backup facilities for surgical abortion or medical emergency, such as transfusions.

Where can mifepristone be provided?
Locations can include: private physicians' offices, abortion clinics, and hospitals.

How much will mifepristone cost, after it is in general distribution?
That has not yet been determined. The general feeling is that the cost of medical abortion will be about the same as surgical abortion. The true cost of the process is much more than the cost of the pills; it

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includes staff, training, facilities, and insurance.

When will mifepristone be available in the US?
The Population Council hopes to gain FDA approval for marketing in 1996.

How were clinics selected for the trials?
The Population Council looked for clinics that could provide: scientific investigators with experience in conducting clinical trials or the ability to work under trial conditions; staff experienced in providing high quality abortion services; routine vaginal ultrasound to determine duration of gestation; adequate waiting and rest rooms; sensitive counseling including provision of contraception; sufficient numbers of clients to enroll volunteers within a few months; good record keeping and follow up; and backup emergency care. Clinics also had to meet legal and insurance requirements. Each potential clinic was inspected by Council monitors.

The Council also attempted to obtain variations in the type of facility (free-standing, hospital-based, feminist health center, Planned Parenthood), geographic location, and type and volume of clientele. Because of the need to limit the number of sites, many excellent clinics were unable to participate in the trials.

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The Population Council, Inc. seeks to help improve the wellbeing and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council ▪analyzes population issues and trends; ▪conducts biomedical research to develop new contraceptives; ▪works with public and private agencies to improve the quality and outreach of family planning and reproductive health services; ▪helps governments to influence demographic behavior; ▪communicates the results of research in the population field to appropriate audiences; and ▪helps build research capacities in developing countries. The Council, a nonprofit, nongovernmental research organization established in 1952, has a multinational Board of Trustees; its New York headquarters supports a global network of regional and country offices.

October 1994

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(The physicians, public health specialists, public policy people, and women's health advocates listed below will be happy to provide you information and expert opinions on mifepristone and abortion services in the US)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Washington, D.C. 20201

MEMORANDUM FOR [redacted]

FROM: [redacted]

SUBJECT: Population Council Studies on RU-486--Information Update

We have been notified by the Population Council that it plans to announce on Thursday, October 27, that the clinical trials of RU-486 as an abortifacient are underway. We have prepared the attached summary to provide you information on these studies. Please let me know if you have any questions.

Attachment

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Update on Medical Abortion

On Thursday, October 27, 1994, in New York City, the Population Council will hold a news conference to announce that clinical trials of the abortifacient mifepristone (known in Europe as RU-486) have begun in the United States. The clinical trials became possible after the Department of Health and Human Services earlier this year helped arrange a transfer of the drug's patent rights to the Population Council, a nonprofit research organization involved in reproductive health and population issues. The clinical trials will be conducted under a protocol which has been reviewed and approved by the FDA.

The clinical trials are designed to determine the safety, effectiveness, acceptability, and feasibility of using mifepristone and prostaglandin to induce a medical abortion. Mifepristone works to interrupt an early pregnancy, and the prostaglandin -- which is administered 48 hours later -- causes the uterus to contract and expels the fertilized egg.

The combination of mifepristone and prostaglandin will be tested in 2100 American women over the age of 18 at more than a dozen sites around the United States. Clinics were selected on the basis of their ability to provide experienced scientific investigators and high quality abortion services. Trial locations include hospital-based clinics, Planned Parenthood and feminist health center facilities, and free-standing abortion clinics.

The Population Council does not intend to identify the trial sites, but individual clinics and women may choose to identify themselves.

Mifepristone in combination with a prostaglandin is approved for use in France, the United Kingdom, and Sweden. It has been used in more than 150,000 women in those countries.

As part of an agreement reached last year with Roussel-Uclaf, the Population Council is conducting the U.S. clinical trials of mifepristone and has agreed to find a manufacturer for the drug. The Population Council has also announced its intention to seek marketing approval from the FDA for mifepristone.

Other Medical Treatments

In a related matter, there has been considerable publicity recently of another method of medical abortion. The anti-metabolite drug methotrexate is being clinically tested, in combination with a prostaglandin, as an abortifacient by Dr. Mitchell Creinin and his colleagues under FDA-approved protocols at three sites around the U.S. Last week Dr. Creinin published the results of his most recent study of this drug in the Journal of the American Medical Association.

Although the preliminary results are somewhat promising, this combination has only been studied in approximately 40 women. The very limited data to date suggest that this regimen is significantly less effective than the mifepristone-prostaglandin combination that is being tested in the Population Council clinical trials. Dr. Creinin and his colleagues have urged physicians not to use this experimental treatment outside of clinical trials.

In the meantime, Dr. Richard Hausknecht, a New York City obstetrician-gynecologist, has been promoting and using the methotrexate-prostaglandin combination in his own private practice. Dr. Hausknecht has granted extensive interviews with major national newspapers and television programs, and he has distributed detailed information about his use of these drugs to thirty or forty physicians around the U.S.

Although the FDA encourages research into medical alternatives to surgical abortion, the agency has told Dr. Hausknecht of its regulatory requirement that his study be carried out only under FDA-approved clinical trials. The FDA regards the methotrexate-prostaglandin combination as experimental and has urged women not to allow this combination to be used for pregnancy termination unless the research is being carried out in an FDA-approved clinical trial.

FDA is concerned that women understand that this drug regimen is experimental -- not a proven treatment. FDA also believes that women deserve the assurance that any clinical research on this drug combination has been scrutinized by an Institutional Review Board, which concerns itself with ethical issues in clinical trials.

The FDA and the Department of Health and Human Services will continue to support research into medical alternatives to surgical abortion. The study of mifepristone and prostaglandin being carried out by the Population Council has been properly designed, and the FDA is confident that women participating in it will understand that they are undergoing an experimental procedure. FDA can offer no such assurances about Dr. Hausknecht's treatment regimen using methotrexate and prostaglandin.

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Food and Drug Administration
Rockville MD 20857

October 25, 1994

TO: The Secretary

FROM: Commissioner of Food and Drugs

SUBJECT: Population Council Studies on RU-486--
Information

The purpose of this memorandum is to provide the Secretary with information regarding the Population Council's plan to announce on Thursday, October 27, that the clincial trials on RU-486 as an abortifacient are under way.

Attached at Tab A is a summary that explains the nature of these studies and the fact that they are not related to the methotrexate/misoprostol studies that were recently publicized by Dr. Hausknecht. Attached at Tab B are talking points and at Tab C, a list of questions and answers.

David A. Kessler, M.D.

Attachments
Tab A - Summary Update on Medical Abortion
Tab B - Talking Points
Tab C - Questions and Answers

cc: Assistant Secretary for Health

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94-9622

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Update on Medical Abortion

On Thursday, October 27, 1994, in New York City, the Population Council will hold a news conference to announce that clinical trials of the abortifacient mifepristone (known in Europe as RU-486) have begun in the United States. The clinical trials became possible after the Department of Health and Human Services earlier this year helped arrange a transfer of the drug's patent rights to the Population Council, a nonprofit research organization involved in reproductive health and population issues. The clinical trials will be conducted under a protocol which has been reviewed and approved by the FDA.

The clinical trials are designed to determine the safety, effectiveness, acceptability, and feasibility of using mifepristone and prostaglandin to induce a medical abortion. Mifepristone works to interrupt an early pregnancy, and the prostaglandin -- which is administered 48 hours later -- causes the uterus to contract and expels the fertilized egg.

The combination of mifepristone and prostaglandin will be tested in 2100 American women over the age of 18 at more than a dozen sites around the United States. Clinics were selected on the basis of their ability to provide experienced scientific investigators and high quality abortion services. Trial locations include hospital-based clinics, Planned Parenthood and feminist health center facilities, and free-standing abortion clinics.

The Population Council does not intend to identify the trial sites, but individual clinics and women may choose to identify themselves.

Mifepristone in combination with a prostaglandin is approved for use in France, the United Kingdom, and Sweden. It has been used in more than 150,000 women in those countries.

As part of an agreement reached last year with Roussel-Uclaf, the Population Council is conducting the U.S. clinical trials of mifepristone and has agreed to find a manufacturer for the drug. The Population Council has also announced its intention to seek marketing approval from the FDA for mifepristone.

Other Medical Treatments

In a related matter, there has been considerable publicity recently of another method of medical abortion. The anti-metabolite drug methotrexate is being clinically tested, in combination with a prostaglandin, as an abortifacient by Dr. Mitchell Creinin and his colleagues under FDA-approved protocols at three sites around the U.S. Last week Dr. Creinin published the results of his most recent study of this drug in the Journal of the American Medical Association.

Although the preliminary results are somewhat promising, this combination has only been studied in approximately 40 women. The very limited data to date suggest that this regimen is significantly less effective than the mifepristone-prostaglandin combination that is being tested in the Population Council clinical trials. Dr. Creinin and his colleagues have urged physicians not to use this experimental treatment outside of clinical trials.

In the meantime, Dr. Richard Hausknecht, a New York City obstetrician-gynecologist, has been promoting and using the methotrexate-prostaglandin combination in his own private practice. Dr. Hausknecht has granted extensive interviews with major national newspapers and television programs, and he has distributed detailed information about his use of these drugs to thirty or forty physicians around the U.S.

Although the FDA encourages research into medical alternatives to surgical abortion, the agency has told Dr. Hausknecht of its regulatory requirement that his study be carried out only under FDA-approved clinical trials. The FDA regards the methotrexate-prostaglandin combination as experimental and has urged women not to allow this combination to be used for pregnancy termination unless the research is being carried out in an FDA-approved clinical trial.

FDA is concerned that women understand that this drug regimen is experimental -- not a proven treatment. FDA also believes that women deserve the assurance that any clinical research on this drug combination has been scrutinized by an Institutional Review Board, which concerns itself with ethical issues in clinical trials.

The FDA and the Department of Health and Human Services will continue to support research into medical alternatives to surgical abortion. The study of mifepristone and prostaglandin being carried out by the Population Council has been properly designed, and the FDA is confident that women participating in it will understand that they are undergoing an experimental procedure. FDA can offer no such assurances about Dr. Hausknecht's treatment regimen using methotrexate and prostaglandin.

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Talking Points
on Medical Alternatives to Surgical Abortion

- Abortion is legal in the U.S. If there is a safe and effective medical alternative to surgical abortion, American women should have access to it.

- The Department of Health and Human Services encourages and supports research into medical alternatives to surgical abortion.

On Mifepristone (RU-486) and Prostaglandin: the Population Council Trials

- The combination of mifepristone and a prostaglandin has been well studied in European clinical trials.

- Clinical trials of this combination in the U.S. represent an significant milestone. The Population Council trials are being conducted in accordance with the FDA regulations concerning drug testing. They have been reviewed by independent Institutional Review Boards to ensure that the research is conducted ethically.

- These clinical trials are designed to answer the fundamental question of whether the drugs are safe and effective in the U.S. medical setting.

- If a sponsor comes forward with data on the safety and effectiveness of mifepristone and prostaglandin for termination of early pregnancy, the Food and Drug Administration is committed to reviewing the data promptly and thoroughly.

On Methotrexate and Prostaglandin Dr. Creinin and Dr. Hausknecht

- The Food and Drug Administration can offer no assurances that the combination of methotrexate and the prostaglandin misoprostol for termination of early pregnancy is either safe or effective.

- The FDA continues to regard this regimen as experimental.

- No clinical trial of this combination has yet provided definitive data on safety and effectiveness.

- The FDA urges women not to allow the combination of methotrexate and misoprostol to be used for pregnancy termination unless this research is being carried out in an FDA-approved clinical trial.

- The FDA has reviewed and approved the design of studies being carried out by Dr. Mitchell Creinin at —— U.S. locations.

- Individual physicians such as Dr. Richard Hausknecht should not be investigating the use of this combination in their clinical practice without FDA approval.

- The FDA's concerns involve both patient safety and informed consent. Clinical investigation of new drugs or new uses of approved drugs must be carried out under the FDA's formal IND (Investigational New Drug) process.

- Research conducted under an IND must be reviewed both by the FDA and by an independent Institutional Review Board.

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The Population Council

One Dag Hammarskjold Plaza, New York, New York 10017

Mifepristone and Prostaglandin
CLINICAL TRIALS

General information about medical abortion and the clinical trials

What is the purpose of the clinical trials?
The purpose of these trials is to determine the safety, efficacy, acceptability, and feasibility of mifepristone plus prostaglandin in inducing abortion, when administered to women with amenorrhea up to 63 days. In France the mifepristone/prostaglandin combination is used to terminate pregnancies in women with amenorrhea of 49 days or less, but in the United Kingdom and Sweden, the combination is used in women with amenorrhea up to 63 days. The trials will reinforce the French data and subsequent experience and perhaps extend the window of effectiveness from 49 to 63 days of amenorrhea.

How does mifepristone work?
Mifepristone is an antiprogestin. One of its actions is to interrupt pregnancy in its early stages. It does this by blocking the action of the natural hormone, progesterone, which prepares the lining of the uterus for a fertilized egg and then maintains the pregnancy. Without the effect of progesterone, the lining of the uterus softens, breaks down, and menstruation begins. Any fertilized egg is expelled through menstruation. Prostaglandins are natural substances made by the lining of the womb during menstruation. The prostaglandin works by causing contractions of the uterus, expelling a fertilized egg.

Where has mifepristone been used?
Since 1981, women in 20 countries (including the United States) have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. All the studies have shown mifepristone to be safe and effective. Government regulatory agencies in France, Great Britain, China, and Sweden approved the drug for marketing, following clinical studies like the one being conducted in the United States. In Europe, over 150,000 women have used mifepristone as a medical abortifacient in combination with various prostaglandins: injectable, vaginal suppository, or oral.

How many women have used the mifepristone/oral prostaglandin combination?
In Europe, there is now an accumulated experience with over 52,000 women who have received mifepristone followed 48 hours later by the oral prostaglandin, misoprostol, at the dose to be used in the U.S. trials. A study published in the *New England Journal of Medicine* in May 1993 showed the combination of mifepristone and oral prostaglandin to be effective "for the termination of early pregnancy in terms of success, tolerance, safety, and practicality." The small dosage of oral prostaglandin taken following use of mifepristone is less than the dosage taken every day by those who use the medication for ulcers.

Do all countries use the same prostaglandin?
No. French women have used mifepristone and an oral prostaglandin since May 1992. The French program originally used both injectable and suppository prostaglandins. English and Swedish women currently use a suppository form of prostaglandin.

Telephone: (212) 339-0500 Telex: 9102900660 POPCO Facsimile: (212) 755-6052 Cable: POPCOUNCIL NEW YO

Why combine mifepristone with another drug?
Studies have shown that, by itself, mifepristone is effective 65 to 80 percent of the time, depending on how early it is taken in a pregnancy. When used with a small dose of prostaglandin, the combination is effective in approximately 95 percent of women.

What is the French experience with medical abortion?
France has the most extensive experience with the mifepristone/prostaglandin combination. Mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion. About 70 percent of eligible women--those with less than 49 days of amenorrhea--have selected medical abortion over surgical abortion. Overall, this means that 30 percent of all abortions in France are medical abortions. There has been no increase in the total number of abortions in France since the method was introduced in 1989.

A few studies have been undertaken to determine women's attitudes. The vast majority of women who have chosen this method have been satisfied. In one study of 174 French women, 94 percent said they were satisfied with this form of abortion. They liked the fact that there was no surgery or anesthesia, that the method is non-invasive, that it takes place earlier in a pregnancy than a surgical abortion, and is more "natural." It also puts the abortion procedure more in the hands of the women than the doctor. Not every woman will prefer medical abortion. Some women prefer the surgical method because it is over quickly.

Has the regimen caused any deaths?
There have been no serious heart conditions in the 52,000 women using the mifepristone/oral prostaglandin combination of drugs for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack, occurred during medical abortion following injection of a prostaglandin. These complications have been most often associated with patients who were heavy smokers. There is no evidence that the oral prostaglandin--a different class of prostaglandin widely prescribed for long-term use in the prevention and treatment of peptic ulcer disease--is associated with any such cardiovascular side effects.

Beginning in May 1992 France replaced the injection with the oral prostaglandin. There have been no complications or deaths since. Women who are over 35 and are heavy smokers are not good candidates for the mifepristone/oral prostaglandin regimen.

Are there any long-term health effects from this combined regimen?
In 10 years of clinical use, there is little evidence of risk with mifepristone. It is believed such a risk is unlikely because the drug causes very few side effects; exposure is so brief; the dosage is small; and most of the drug is eliminated from the body within two or three days. The oral prostaglandin has been used safely for gastric ulcers for many years. The dosage taken in conjunction with mifepristone for medical abortion is low.

What is the effect of mifepristone on a woman's future fertility?
There are no indications that use of mifepristone to end a pregnancy has affected a woman's ability to have a baby when she was ready. Women who have taken mifepristone have been able to conceive and subsequently bear healthy children. Having an early medical or surgical abortion has not been proven to make future miscarriage more likely.

MIF 003627

Does mifepristone cause fetal deformities?
There is no evidence that it does. But little is known about the effect of mifepristone or prostaglandin on a developing embryo or fetus. Therefore, women ought to have surgical abortions when a medical abortion fails. Only a few instances are known where women decided to continue with their pregnancies after taking mifepristone to produce an abortion. In all but one case, a normal baby was delivered. In that case, a sonogram in the second trimester indicated fetal abnormalities and the woman underwent a surgical abortion. It was not known whether the abnormalities were related to mifepristone. While concern over fetal abnormalities is valid, one should also remember that 6 percent of all newborns have developmental congenital abnormalities, half of them serious.

Why is mifepristone effective only in the earliest weeks of pregnancy?
In the first few weeks following fertilization and implantation, the ovaries produce progesterone. By the ninth and tenth week, the placenta produces progesterone in larger amounts, so that antiprogestins are unable to compete with the natural hormone.

What happens if the drugs fail to end a pregnancy?
The mifepristone/oral prostaglandin combination fails in about four of every 100 cases. Failures include both ongoing pregnancies (1 in 100) and incomplete abortions (3 in 100). When that happens, the abortion should be completed through surgical means, generally vacuum aspiration or curettage. Women in the clinical trial will consent in advance to surgical abortion in case medical abortion fails.

Can a woman change her mind after taking the first drug, and before taking the second?
Good counseling will make sure a woman know that she may risk harming her fetus if she continues her pregnancy after taking mifepristone. But that is her decision. Although the informed consent makes it clear to women that they should not continue their pregnancies after taking mifepristone, no one can or will force a woman to have an abortion.

Why would a woman choose medical abortion instead of surgical abortion?
A woman might choose medical abortion over surgical abortion because:

- It can be used in the earliest weeks following fertilization
- It requires no invasive procedure or surgery
- It requires no anesthesia
- Side effects tend to be moderate
- It does not carry risk of uterine perforation or injury to the cervix
- It has the potential for greater privacy
- Some women feel they have greater control over their own bodies when they use the medical abortion procedure

Why would a woman choose surgical abortion over medical abortion?
A woman might choose surgical abortion over medical abortion because:

- It requires fewer office visits and is over quickly
- It is slightly more effective than medical abortion, where four of every 100 women require surgical abortion
- The woman notices less blood loss and is unaware of the passing of the product of conception

Why might a woman want an early abortion?
A woman can choose medical abortion as soon as she suspects she is pregnant and the pregnancy can be confirmed. If she waited for a surgical abortion, she would have to wait several weeks longer.

Why would a woman choose a method that is not as effective as surgical abortion?
Medical abortion is not as effective as surgical abortion. Women are told that they run the risk of an incomplete abortion--this happens with natural miscarriages--or even an ongoing pregnancy. Despite this, many women choose medical abortion because they feel more in control, because it takes place early in a pregnancy, because it's similar to a natural miscarriage and they do not have to undergo surgery.

Will availability of mifepristone make having an abortion too easy?
Decisions about having an abortion are never easy. Medical abortion is not an easy method. Although it involves taking pills, and no surgery, it is a slower procedure, more like a natural miscarriage.

What is the protocol for the trials?
If the pregnancy has been confirmed, and the woman has not had menstrual bleeding for up to 63 days, she may be eligible to participate in these trials. The regimen requires at least three visits: The first encompasses counseling on available options; full obstetrical and medical history; physical examination; and determination of length of pregnancy via vaginal ultrasound. If there are no contraindications to mifepristone use, the woman will swallow three tablets, each 200 mg, and remain under observation for 1/2 hour. The second visit involves a return to the clinic 36 to 48 hours later; the woman will ingest two 200 microgram tablets of oral prostaglandin under supervision, and remain at the clinic for four hours under the observation of clinic staff. About two-thirds of women abort during this four-hour period. Uterine bleeding will continue for several days, possibly for 4-16 days. The third, follow-up, visit takes place 12 days later (14 days after taking mifepristone), to ensure the abortion is complete. If the clinician is not sure whether abortion has been complete, blood tests or ultrasound will be taken. If abortion is not complete at this time, vacuum curettage will be performed.

What are the side effects from mifepristone and oral prostaglandin use?
Some women do not experience any physical discomfort after taking mifepristone; others have light uterine bleeding in the two days before taking the prostaglandin. The side effects of mifepristone appear to be similar to the side effects of "morning sickness" of a normal pregnancy -- nausea, headache, weakness, and fatigue.

Side effects are more common after taking the oral prostaglandin. They include:

- Cramps and abdominal pain, similar to those associated with a very heavy menstrual period. They are a normal, expected part of the abortion process; some 80 percent of women get them.
- Nausea, vomiting, and diarrhea, sometimes requiring medication
- Uterine bleeding: similar to a heavy period and lasting at least one week, or bleeding and spotting that is not heavy but can last for one to three weeks. In rare cases, if uterine bleeding is extremely heavy, the woman may require surgical abortion and/or blood transfusion.

What is the risk of hemorrhage requiring blood transfusion?
Heavy uterine bleeding can occur, but is rare. Severe hemorrhage sometimes necessitates a blood transfusion. In France, about one in 1,000 women require a transfusion.

MIF 003629

How do you determine the age of a pregnancy?
All pregnancies are dated from the first day of the woman's last menstrual period (LMP). This is known as the duration of amenorrhea. However, those concerned with the actual age of the embryo should realize that there are usually two weeks between the time a woman's menstrual period starts to the time she ovulates. Therefore, 49 days LMP means a 35-day-old embryo, and 63 days LMP means a 49-day-old embryo.

How many women will be taking part in these trials?
Up to 2100 women will volunteer for these trials, at locations around the country.

How will patients be selected for the clinical trials?
Women seeking abortions will go to available providers; at some locations women will be told, "Today you have a choice." Counseling, physical exams, and determination of the age of gestation will be similar to surgical abortion.

How will women find out where the method is available?
Women seeking medical abortion will find out about availability through a variety of means: some clinics may advertise; some may announce they are trial sites or be quoted in news stories. Health care providers in other facilities may make referrals. Some women will hear about it from friends. The Population Council will not refer patients to individual clinics.

Why would women want to participate in this experiment?
Clinical trials like these are required for all FDA approvals. Women who volunteer to participate in these trials are carefully screened and are given sensitive and accurate counseling. In addition, the volunteers know they are participating in a study that will help make this drug available to other American women. Besides, this is not an untested drug. Over 150,000 women have used this drug in Europe, and over 52,000 of them have used the same combination of drugs that is used in the U.S.

Will teenagers be eligible for mifepristone?
Only women 18 and older will be able to participate in the trials.

How much will it cost to take part in the trials?
Women who volunteer to take part in a clinical trial of an experimental drug do not have to pay for it. Neither are they paid to participate.

After mifepristone is approved for marketing, who will be able to provide it?
The mifepristone regimen will be able to be provided by any physician qualified to determine the age of a pregnancy and diagnose the possibility of an ectopic pregnancy. The physician also must be trained and licensed to perform abortions, and have access to backup facilities for surgical abortion or medical emergency such as transfusions.

Where can mifepristone be provided?
Locations can include: private physicians' offices; abortion clinics, and hospitals.

How much will mifepristone cost, after it is in general distribution?
That has not yet been determined. The general feeling is that the cost of medical abortion will be about the same as surgical abortion. The true cost of the process is much more than the cost of the pills: it

includes staff, training, facilities, and insurance.

When will mifepristone be available in the US?
The Population Council hopes to gain FDA approval for marketing in 1996.

How were clinics selected for the trials?
The Population Council looked for clinics that could provide: scientific investigators with experience in conducting clinical trials or the ability to work under trial conditions; staff experienced in providing high quality abortion services; routine vaginal ultrasound to determine duration of gestation; adequate waiting and rest rooms; sensitive counseling including provision of contraception; sufficient numbers of clients to enroll volunteers within a few months; good record keeping and follow up; and backup emergency care. Clinics also had to meet legal and insurance requirements. Each potential clinic was inspected by Council monitors.

The Council also attempted to obtain variations in the type of facility (free-standing, hospital-based, feminist health center, Planned Parenthood), geographic location, and type and volume of clientele. Because of the need to limit the number of sites, many excellent clinics were unable to participate in the trials.

For information, contact:
Sandra Waldman, Director, Office of Public Information
212/339-0525

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The Population Council, Inc. seeks to help improve the wellbeing and reproductive health of current and future generations around the world and to help achieve a humane, equitable, and sustainable balance between people and resources. The Council ■analyzes population issues and trends; ■conducts biomedical research to develop new contraceptives; ■works with public and private agencies to improve the quality and outreach of family planning and reproductive health services; ■helps governments to influence demographic behavior; ■communicates the results of research in the population field to appropriate audiences; and ■helps build research capacities in developing countries. The Council, a nonprofit, nongovernmental research organization established in 1952, has a multinational Board of Trustees; its New York headquarters supports a global network of regional and country offices.

October 1994

MIF 003631

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

August 14, 1995

NOTE TO: _____

The Secretary is scheduled to attend the Fourth World Conference on Women, which will take place in Baijing, China, September 4-15, 1995. U.N. Ambassador, Madeleine Albright, will head the delegation, which will also include EPA Administrator, Carol Browner. The conference is expected to draw more than 35,000 participants worldwide.

Thank you for your cooperation.

/S/ /S/

Attachments

cc: _____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 14, 1994

Dr. Andre Ullman
Roussel Uclaf
102, route de Noisy
93235 Romainville Cedex
FRANCE

Dear Dr. Ullman:

The Food and Drug Administration asks that Roussel Uclaf provide The Population Council access to, and the ability to copy and submit to the United States Food and Drug Administration, any information relevant to the use of mifepristone (RU-486) for the termination of early pregnancy. This request includes case report forms, electronic data bases, synthesis and manufacturing information, and any other information required by United States laws and regulations to be included in a New Drug Application for mifepristone.

We would appreciate your prompt consideration of this request.

Sincerely yours,

/S/

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94-8442

MIF 003633

INSTITUTE OF MEDICINE
NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE WASHINGTON, D. C. 20418

KENNETH I. SHINE, M. D.

August 6, 1993

Department of Health and Human Services
Hubert H. Humphrey Building, Room 716-G
200 Independence Avenue, S.W.
Washington, DC 20201

Dear —

I am pleased to invite you to a dinner and briefing on the Institute of Medicine's forthcoming report, "Clinical Applications of Mifepristone (RU 486) and Other Antiprogestins: Assessing the Science and Recommending a Research Agenda" on Wednesday, September 8, 1993 at 6:30 pm.

The IOM report evaluates the current state of the science regarding clinical uses of antiprogestins and gives recommendations concerning future research on the potential clinical use of antiprogestins in the United States.

We expect the report to be released publicly on September 8, 1993, to coincide with this dinner and briefing. At the dinner the chairman of the committee, Leslie Z. Benet, along with several members of the committee will present a brief review of the committee's work and recommendations. The discussion following dinner will provide an opportunity for Administration officials, Members of Congress, agency representatives, foundation representatives, and private sector leaders to discuss aspects of the report with its authors. I hope you will join me on Wednesday evening, September 8, for a small reception at 6:30 p.m. in the Rotunda, with dinner following at 7:15 p.m. in the Members' Room of the National Academy of Sciences at 2101 Constitution Avenue, N.W. Please use the Constitution Avenue entrance.

We hope you will be able to attend this special event. Please RSVP to Kathi Hand at 202-334-1601 by August 27.

Yours sincerely,

Kenneth I. Shine, M.D.
President

cc: Kathi Hand

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The Saturday Evening Post
SOCIETY

Cory SerVaas, MD
Editor
THE SATURDAY EVENING POST

DEX TRANSMISSION SHEET

TO: LOUIS SULLIVAN

FROM: CORY SERVAAS M.D.

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MIF 003635

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The Saturday Evening Post
·SOCIETY·

Cory SerVaas, MD
Editor
THE SATURDAY EVENING POST

October 14, 1992

Secretary Jack Kemp
U.S. Department of Housing and Urban Development
Washington, DC 20410

Dear Jack:

You could help our GOP ticket win seats this year if you could just persuade the President and Dan Quayle to say:

"We have a win-win solution to the abortion problem.

"We have instructed the FDA to approve for immediate use as a contraceptive, a pill that will prevent conception immediately after coitus."

It will prevent conception if taken promptly and it has no side effects other than causing a woman to be late for her period. This isn't a problem as she can know she isn't pregnant with the home pregnancy kits.

Yes, this contraceptive CAN prevent the sperm from reaching the egg so that even the most purist of the hard-rock fundamentalists can be sure they are okay in using it as long as they agree that contraception is okay.

It is more effective than the intrauterine device and safer.

This one-time pill would be inexpensive for the poor women who need it most. It could wipe out the need for abortions by preventing pregnancies from occuring in a most convenient manner.

Please, Jack, use your influence to get the GOP to get credit for putting this mifeprisone into the hands of the women who want it.

Division of the Benjamin Franklin Literary & Medical Society
1100 Waterway Boulevard • Indianapolis, Indiana 46202 • (317) 636-8881 • FAX (317) 637-0126

As a female and a physician, I can tell you that my women friends are balking over this issue and when Bill Clinton and Hillary see the obvious reasons for getting it approved by the FDA fast we'll look like slow learners.

We could scoop them at it. It is new because we didn't know it would work to prevent pregnancy before. Now we know! Let's act!

I have talked with the authors of these journal articles and to David Baird in England. I am told that there are new improvements of this pill that are ready. We need never refer to the old RU-486.

If we could get the FDA's approval before the election, it might make the difference.

Very Cordially,

Cory SerVaas, M.D.

Cory SerVaas, M.D. gc

INSTITUTE OF MEDICINE
NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE WASHINGTON, D.C. 20418

SEP 16 3 10 PM '93

DIVISION OF
HEALTH SCIENCES POLICY

FAX: 202/334-1566

September 13, 1993

MEMORANDUM

TO: Members of the Forum on Drug Development

FROM: Joe Cassells, Director
Forum on Drug Development

SUBJECT: IOM Report *Clinical Applications of Mifepristone, RU 486, and Other Antiprogestins*

Les Benet's Committee on Antiprogestins: Assessing the Science, has recently released their final report. Enclosed, please find a copy of the report summary. If you would like a copy of the full report, please contact Jay Ball, (202) 334-2526.

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ON ORIGINAL

43-4516

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

November 30, 1995

TO: [redacted] OLA

FROM: [redacted]
FDA Executive Secretariat

SUBJECT: Congressional Document Request from Rep. Coburn Regarding RU-486--
TRANSMITTAL

This is in response to your memo, dated November 20, 1995 for copies of documents relating to communications concerning RU-486 (mifepristone), requested in a November 10, 1995 letter from Representative Tom Coburn. Per our discussion, [redacted], the following documents are attached:

Tab A - RU-486 documents previously released in response to an FOI request (#93 47009) in 1994 (with index for your information). These records have already been redacted and are releasable.

Tab B - Releasable responsive documents received by FDA Exec Sec since the above referenced FOI response was issued. These are FOI releasable.

Tab C - [redacted] documents received by FDA Exec Sec since the above referenced FOI response was issued. These are provided for your information.

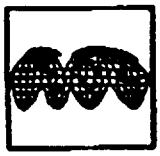
[redacted]

[redacted]

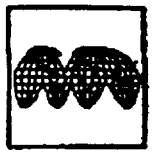
/S/

[redacted]

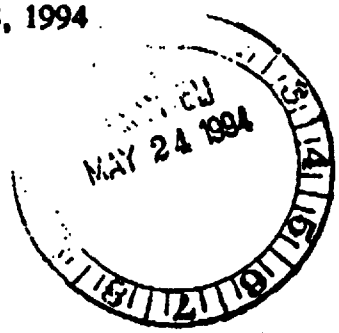
Attachments



Every Pregnancy A Wanted Pregnancy



May 18, 1994



Ms. Margaret Catley-Carlson, President
The Population Council
1 Dag Hammarskjold Plaza - 9th Floor
New York, New York 10017

Dear Ms. Catley-Carlson:

As chair and on behalf of both the Society of Physicians for Reproductive Choice and Health and the Scientific Advisory Board of the Delta Group, I wish to express our congratulations and thanks for the tireless efforts and successful negotiation by the Population Council, Dr. David Kessler and the Food and Drug Administration, Secretary Donna Shalala and their people in obtaining the patent rights for RU 486 from Roussel Uclaf. This is a historic accomplishment that now challenges all of us to advocate, counsel and implement a delivery system that will permit RU 486 and its biologic properties to be pharmacologically available for personal choice in conception control, effective family planning, and the health care of women.

The Society of Physicians for Reproductive Choice and Health is a national organization with international aspirations. We have been granted a 501(c)(3) status. Our membership is committed to developing a reproductive health care educational and advocacy program that will involve physicians, medical students and concerned scientists. The membership has a responsibility to promote an ethical patient-doctor relationship consistent with a state of physical, mental and social well being for each individual. We believe there is a need for such leadership to encourage public communication and a realistic awareness of the biology of human reproduction and human sexuality within the context of emerging contraceptive technology and to support the concept of reproductive freedom and personal choice. There is no intent in any of these responsibilities to impose a coercive element and there is a conscious sensitivity for ethnic, cultural, and religious diversity.

The Delta Group and its Scientific Advisory Board are equally committed to the exploitation of the biologic properties of RU 486 and any subsequent analogs that may be synthesized for the benefit of humankind. I, personally, was responsible for the initial recruitment of Norman Hinerfeld and his colleagues to undertake a leadership role in the organization of a corporate structure that would have the funding, the energy, the know-how, and the temerity to manufacture and distribute RU 486 if the Population Council obtained a contract. You and your colleagues are acquainted with the thoroughness of Delta's accomplishments that have been necessary to develop an ethical and financially stable company.

Albert Einstein College of Medicine / Ullmann Building - Room 109
1300 Morris Park Avenue, Bronx, NY 10461 / Telephone Number: 718-430-2691 / Fax Number: 718-430-8720

Hinerfeld and his colleagues and the membership of the Scientific Advisory Board recognize a private-public trust responsibility if we are selected to join the Population Council and assist in the implementation of your objectives.

We hope the Population Council will recognize the Delta Group as a partner in your population oriented reproductive health care work.

Sincerely,

Seymour L. Romney, M.D.
Professor Emeritus

cc: Mr. Norman Hinerfeld
Dr. David Kessler
Hon. Donna Shalala

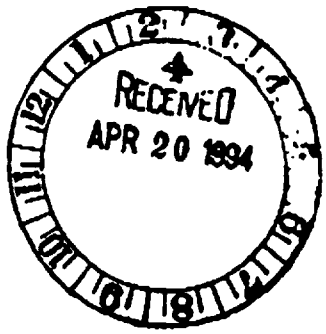
SLR/et

SP51894

SWIDLER & BERLIN
CHARTERED

LESTER S. HYMAN
OF COUNSEL

DIRECT DIAL
(202)424-7509



19 April 1994

Dear Dr. Tessler —

Just a brief note to tell you how much I enjoyed meeting you at our recent meeting with Secretary Shalala to discuss the RU-486 issue.

I know that my clients at Roussel were gratified by your willingness to work with them to solve the outstanding issues, and Professor Ottis is contacting you directly to discuss next steps.

My partner ——— and I stand ready to be of every possible assistance. We look forward to seeing you again soon.

Always sincerely,

Lester S. Hyman

3000 K STREET, N.W. ■ SUITE 300
WASHINGTON, D.C. 20007-5116
(202)424-7500 ■ TELEX 701131 ■ FACSIMILE (202)424-7643

The Feminist Majority Foundation

The Secretary Has Seen

Kessler
Neville
Rock
Kramer

May 19, 1994

Secretary Donna Shalala
Department of Health and Human Services
200 Independence Avenue
Washington, D.C. 20201

Donna

Dear Secretary Shalala,

I wanted to thank you for your leadership in bringing RU 486 to the United States.

The announcement of the transfer of RU 486 patent rights from Roussel Uclaf to the Population Council was truly historic. We understand from all parties that your strong position in favor of RU 486 and your courage in establishing a deadline for action by Roussel Uclaf were largely responsible for the signing of the contract on Monday.

Because of your work not only will women soon have access to RU 486 as a method of early abortion, but the logjam on clinical trials on the other uses of RU 486 has been broken.

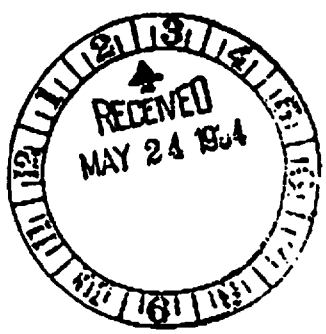
We look forward to working with you to make sure that the clinical trials, identification of a manufacturer, New Drug Application, and Food and Drug Administration approval proceed as quickly as possible. We also hope that expanded clinical trials on RU 486 as a treatment for breast cancer, endometriosis, meningioma, Cushing Syndrome, and fibroid tumors and as a contraceptive and morning after pill can move forward expeditiously.

RU 486 is long overdue in this country. You have done a great service for American women by ending the delays that have kept this medical breakthrough from the United States.

Sincerely,

Ellie

Eleanor Smeal
President



GJ-5516

1600 Wilson Boulevard, Suite 801, Arlington, VA 22209 • (703) 522-2214 • Fax (703) 522-2219

SWIDLER & BERLIN
CHARTERED

LESTER S. HYMAN
OF COUNSEL

DIRECT DIAL
(202)424-7509

20 May 1994

Dear David —

Thank you so very much for your tremendous dedication of time and talent that helped bring about the historic announcements of May 16th.

I hope there will be other opportunities for us to work together in the future.

Warmest regards —

LS

3000 K STREET, N.W. ■ SUITE 300
WASHINGTON, D.C. 20007-5116
(202)424-7500 ■ TELEX 701131 ■ FACSIMILE (202)424-7643

The Feminist Majority Foundation

May 20, 1994

Food and Drug Administration
Parklawn Building, Rm. 1481
5600 Fisher's Lane
Rockville, MD 20857

Dear ——

I wanted to thank you for your leadership in making RU 486 available to American women.

The announcement of the transfer of RU 486 patent rights from Roussel Uclaf to the Population Council was truly historic. All parties felt that you had played a crucial role in convincing Hoechst AG and Roussel Uclaf to move forward with the Population Council contract.

We look forward to working with you to make sure that the clinical trials, identification of a manufacturer, New Drug Application, and FDA approval proceed as quickly as possible. We also hope that expanded clinical trials on RU 486 as a treatment for breast cancer, endometriosis, meningioma, Cushing's Syndrome, and fibroid tumors and as a contraceptive and morning after pill can move forward expeditiously.

Again, our thanks for your commitment and perseverance. You have done a great service for American women by helping to end the delays that have kept this medical breakthrough from the United States.

For Women's Rights,

Eleanor Smeal

Eleanor Smeal
President

1600 Wilson Boulevard, Suite 801, Arlington, VA 22209 • (703) 522-2214 • Fax (703) 522-2219

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 9, 1994

Docteur Edouard Sakiz
Président du Conseil de Surveillance
Roussel Uclaf
35, Boulevard dès Invalides
75007 Paris, France

Dear Edouard,

I want to thank you very much for your kind letter of May 25. I also want you to know what a pleasure it has been working with you over the past year.

Although we faced some difficult moments together, I recognize that our mutual success was brought about in large part through your personal dedication, hard work, and conviction that RU-486 should be made available to women in this country if it is found to be safe and effective through our regulatory review process. I also want to express my appreciation to others at Roussel Uclaf who made this possible.

If I return to Paris and have an opportunity to visit with you, I will certainly let you know. Until then, my very best wishes to you.

Sincerely yours,

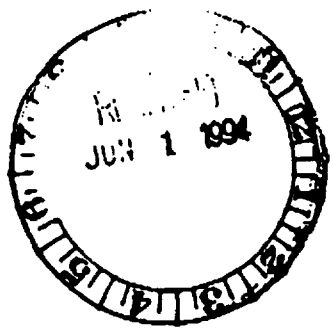
/S/

APPEARS THIS WAY
ON ORIGINAL

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Conseil de Surveillance

Paris, May 25th, 1994



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

Dear Doctor Kessler,

On behalf of all of us at Roussel Uclaf, I write to thank you for your personal concern and attention to the RU 486 project.

Without the involvement of you and ———————, the successful resolution that Secretary Shalala announced on May 16th could not have taken place.

We have been most impressed with your professionalism and dedication. The United States Government is indeed fortunate to have people of your calibre protecting the health and safety of the American people.

On a personal basis, I look forward to working with you again in the future.

Yours sincerely,

APPEARS THIS WAY
ON ORIGINAL

35, Boulevard des Invalides 75007 Paris
Tél. + 33 (1) 40 62 44 28 Fax. +33 (1) 40 62 44 90 Tlx GRUPA 200 675

The Feminist Majority Foundation

May 19, 1994

Secretary Donna Shalala
Department of Health and Human Services
200 Independence Avenue
Washington, D.C. 20201

Dear Secretary Shalala,

I wanted to thank you for your leadership in bringing RU 486 to the United States.

The announcement of the transfer of RU 486 patent rights from Roussel Uclaf to the Population Council was truly historic. We understand from all parties that your strong position in favor of RU 486 and your courage in establishing a deadline for action by Roussel Uclaf were largely responsible for the signing of the contract on Monday.

Because of your work not only will women soon have access to RU 486 as a method of early abortion, but the logjam on clinical trials on the other uses of RU 486 has been broken.

We look forward to working with you to make sure that the clinical trials, identification of a manufacturer, New Drug Application, and Food and Drug Administration approval proceed as quickly as possible. We also hope that expanded clinical trials on RU 486 as a treatment for breast cancer, endometriosis, meningioma, Cushing Syndrome, and fibroid tumors and as a contraceptive and morning after pill can move forward expeditiously.

RU 486 is long overdue in this country. You have done a great service for American women by ending the delays that have kept this medical breakthrough from the United States.

Sincerely,

Eleanor Smeal
President

1600 Wilson Boulevard, Suite 801, Arlington, VA 22209 • (703) 522-2214 • Fax (703) 522-2219

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

June 13, 1994

Mrs. Judie Brown
President
American Life League, Inc.
Post Office Box 1350
Stafford, Virginia 22555

Dear Mrs. Brown:

This is in response to your letter of June 3, 1994, to Dr. David Kessler, requesting information concerning RU-486 (mifepristone).

I have enclosed those documents that you requested that the Agency has in its possession. These are limited to the names and curricula vitae of current voting members of the Center for Drug Evaluation and Research's Fertility and Maternal Health Drugs Advisory Committee and the Center for Devices and Radiological Health's Medical Devices Advisory Committee's Obstetrics-Gynecology Devices Panel. The Agency is not in possession of the other documents that you requested.

This drug, like any other drug, will be studied pursuant to Food and Drug Administration (FDA) regulations, 21 CFR Part 312, and any new drug application for the drug will not be approved unless the drug meets all FDA requirements, 21 U.S.C. §355 and 21 CFR Part 314. We cannot comment on the specific questions you have raised, because the details of any investigational new drug application that have not been disclosed by the sponsor are confidential, in accordance with FDA's regulations.

You also requested information regarding United States policy with respect to medical coverage for injuries incurred by patients who participate in clinical trials. FDA's informed consent regulations require, for research involving more than minimal risk, that each research subject be provided an explanation as to whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained (21 CFR 50.25(a)(6)). We are not aware of any U.S. policy that would require either the clinical investigator or the study sponsor to provide medical coverage for injuries incurred as a result of participation in this type of clinical study. Clearly, a clinical investigator or sponsor may choose to do so, but there is no federal requirement.

Under Agency policy, this drug, as well as any other drug, is to be studied consistent with appropriate ethical, legal, and scientific standards.

Sincerely yours,

151

[ ]

Enclosures

American Life League, Inc.

National Headquarters: P.O. Box 1350, Stafford, VA 22555
(703) 659-4171 • Metro D.C. 690-2049 • Fax (703) 659-2586

RECEIVED
JUN 8 9 52 AM '94
FDA
EXECUTIVE SECRETARIAT

June 3, 1994

Commissioner David A. Kessler, M.D.
U. S. Food and Drug Administration
5600 Fishers Lane, Room 1471
Rockville, MD 20857

Dear Dr. Kessler:

We at American Life League have read with interest of the aggressive role the Clinton administration and you have played in pressuring Roussel-Uclaf to reach an agreement with the Population Council to bring the abortion drug RU-486 to the United States. The history of the Population Council (see below) has made clear that they have a political agenda that places the human rights and health of women at a lesser premium than the goal of curbing reproduction among the poor.

We are deeply concerned about the potential impact of this agenda on the approval process for RU-486, and we are similarly concerned that the aggressive stance of yours and of the the Clinton administration will compromise the ethical and medical standards that should apply in the conduct of RU-486 trials. The Food and Drug Administration's own record in approving the Pill and IUD as initially safe for women who were subsequently harmed by these drugs and devices is hardly reassuring. Moreover, it is troubling in this context that the FDA has a history of relying upon advisors who have a population control agenda.

Because of this, we are asking that you immediately release to the public the following:

* The names and curricula vitae of all FDA advisors of all current members of the FDA's obstetric and gynecological committee;
* The names of the principal investigators conducting the trials for the Population Council or its agent;
* Copies of the informed consent form(s) and related materials to be distributed and/or signed by the women who participate in the RU-486 experiments;
* Information regarding the procedures and oversight the FDA will insist upon to ensure that the group or groups selected for RU-486 trials and experiments will not be lost to follow-up, as happened in the original oral contraceptive trials in Puerto Rico;
* A description of the economic/social characteristics of the women who will participate in the RU-486 trials;

* Information regarding whether any woman under the age of 18 will participate in the RU-486 trials and, if so, whether her parents or guardians will be required to give consent for her participation;
* The medical warnings, if any, that will be given to women in these trials, as well as information regarding any waivers required for participation in RU-486 trials;
* Information regarding U.S. policy with respect to medical coverage of injuries suffered by any women as a result of participation in RU-486 trials;
* A statement as to whether you made any representation or promise to any official or representative of Roussel-Uclaf or other party interested in marketing RU-486 regarding the availability of prostaglandin drugs from Searle, or any other company, to be used in conjunction with RU-486.

Our concerns regarding these issues are based on bitter experience.

It is obvious that prototypical health standards--specifically the injunction against intentional or negligent infliction of physical harm upon an individual--have regularly been overridden where the collective values of the population control community are enthroned as policy guidelines. For example, Planned Parenthood's Dr. Elizabeth Connell, who later became a consultant to an FDA Drug Advisory Committee, stated: "It would be unreasonable to expect those attempting to deal with the exigencies of the population crisis and the agonies caused by unwanted pregnancies to view the pill precisely the same way as medical traditionalists demanding a preparation proved 100 percent effective, safe and devoid of all side effects."[1]

The Population Council's disregard for the health and rights of women has an even older pedigree. I call your attention to a remark by Dr. J. Robert Willson at a 1962 conference sponsored by the Population Council, which was promoting the now discredited IUD. Dr. Willson said: ". . . suppose one [patient] does develop an intrauterine infection and suppose she does end up with a hysterectomy . . . How serious is that for the particular patient and for the population of the world in general? Not very. Perhaps we have to stop thinking in terms of individual patients . . . perhaps the individual patient is expendable in the general scheme of things, particularly if the infection she acquires is sterilizing but not lethal."[2]

Dr. Mary Calderone, Planned Parenthood's Medical Director at that time, said: "It thrilled me to hear a clinician like Dr. Willson talk in terms of public health applications as I, a public health person, would not have dared to talk, particularly in this assembly."[3]

Dr. Jack Lippes, inventor of the FDA-approved Lippes Loop, said: "As you know, I have no reservations about ascending infection. This is not one of the things I worry about."[4]

To put it rather mildly, ascending infection associated with intrauterine devices gave tens of thousands of American women a great deal to worry about. That sorry experience, a result of the indifference of population-control activist physicians, and of the rush to judgment of a sympathetic FDA, should never be repeated. That is why it is of surpassing importance that the FDA insure that the processes, personnel, and protocols involved in the examination of the safety of RU-486 be conspicuous and contemporaneously released to the public now for examination.

For the health and safety of American women, we strongly urge you to proceed forthrightly and in the open, and make a full disclosure of all material relating to the review and potential for approval of RU-486.

Sincerely yours in the Lord of Life,

Judie Brown

(Mrs.) Judie Brown, President
American Life League, Inc.

1 *Family Planning Perspectives*, January 1970.
2 Intrauterine Contraceptive Devices, Proceedings of the Conference. Excerpta Medica Foundation, April-May, 1962, p. 124, 125.
3 Ibid.
4 Ibid.

AMBASSADE DE FRANCE AUX ETATS-UNIS

4101 Reservoir Road, N.W.
Washington, DC 20007
Téléphone: (202) 944-6232
Télécopie: (202) 944-6257

Le Conseiller
pour les Affaires sociales

May 19, 1994

FDA
5600 Fishers Lane
Room 1481
Rockville, MD 20857

Dear ———————

It has been a pleasure seeing you earlier this week on the occasion of the hearing on RU-486.

I thought you might be interested in obtaining a copy of the letter I sent to Commissioner Kessler regarding the French Health Care System.

Best regards,

Pascal CHEVIT, MD, MPH

APPEARS THIS WAY
ON ORIGINAL

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FDA
EXECUTIVE SECRETARIAT

AMBASSADE DE FRANCE AUX ETATS-UNIS

COPY

4101 Reservoir Road, N.W.
Washington, DC, 20007
Téléphone: (202) 944-6232
Télécopie: (202) 944-6257

Le Conseiller
pour les Affaires sociales

May 19, 1994

Dr. David Kessler
Commissioner
FDA
5600 Fishers Lane
Room 11-45
Rockville, MD 20857

Dear Commissioner Kessler:

It was a privilege for me to listen to your testimony regarding RU-486 before the House subcommittee on small business on Monday, May 16.

I fully agree with you that the United States and French Health Care Systems are very different. It is true that there is a much larger government run health care network in France than here.

However, even though the administration is part of most decisions, our mandatory Health Insurance System is not a public entity. It is administered by a board made primarily of representatives of employers and employees.

Moreover, on the delivery side, France is a mix of public and private providers: two thirds of acute care hospital beds are public, one third private. The figures are roughly the opposite for medium and long term hospital beds and almost all physicians in office based practice are in the private sectors.

As far as pregnancy interruption is concerned, there is a government run accreditation process, but private hospitals and clinics are eligible as well as public ones. In 1992 (last year's data is unknown yet), 166,507 interruptions were performed in France: 111,710 in the public sector, 54,797 in the private one, or two thirds in the public, one third in the private sectors.

.../..

The French reality is probably closer to the one in the United States that one could think. This may be of interest in the coming debate on RU-486 distribution and delivery in the United States.

You will find enclosed, for your information, a set of documentation on the French Health Care System.

Respectfully yours,

Pascal CHEVIT, MD, MPH

cc: _____

APPEARS THIS WAY
ON ORIGINAL

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Conseil de Surveillance

Paris, May 30th, 1994

The Honorable Donna E. Shalala
Secretary of the Department of Health
& Human Services
H.H.H. Building - Room 615 F
Washington, D.C. 20201
U.S.A.

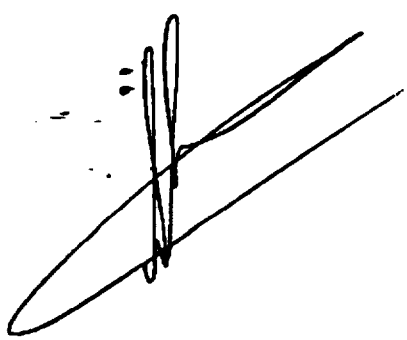
Dear Secretary Shalala,

On behalf of the Roussel Uclaf Group, I would like to express our sincere thanks for your personal involvement and assistance with the RU 486 project.

The successful resolution that you announced on May 16th had been awaited for a very long time by American women, and it gave me tremendous pleasure to witness the enthusiasm that followed the announcement.

Personally, I am very pleased that your Administration has come to this decision after a careful review of the situation, and despite the fact that many obstacles had to be surmounted. I would like to congratulate you on the determination which you showed in these initial steps to make the drug available to American women.

Respectfully yours,



APPEARS THIS WAY
ON ORIGINAL

55, Boulevard des Invalides "Sud" Paris
Tél. : 33 (1) 40 62 44 28 Fax. : 33 (1) [illegible]
Roussel Uclaf, Société Anonyme à Directoire [illegible] Surveillance

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

AUG 13 1992

MEMORANDUM

TO: The Secretary
Through: DS _____
COS _____
ES _____

FROM: Assistant Secretary for Health

SUBJECT: RU-486--BRIEFING

PURPOSE

This memorandum is to provide briefing information on the drug RU-486.

BACKGROUND

RU-486 is approved for abortion in France and England and is not approved for marketing in this country. It is manufactured by the French drug firm Roussel Uclaf, which holds a patent on the starting material for the drug. The manufacturer has not submitted a new drug application to FDA for review and has stated publicly that it will not do so unless the political climate regarding abortion in the United States changes.

Used in combination with a prostaglandin administered 36 to 48 hours later, RU-486 is reported to have an efficacy rate of 98.7% for early first trimester abortions using a single 600 mg dose followed by an injection of the prostaglandin sulprostone. The efficacy rate with another prostaglandin, gemeprost, administered as a vaginal suppository, is reported to be 96.3%. Neither of these prostaglandins is approved for use in this country. However, in April of this year, the regimen in France was changed. Sulprostone is no longer being used and another prostaglandin, Cytotec, which is taken orally and is approved in this country for the prevention of ulcers for patients taking nonsteroidal anti-inflammatory drugs, was added to the regimen. Reports from preliminary data suggest an efficacy of 96% for this regimen.

The medical risks of RU-486 use include uncontrolled bleeding, which can be fatal. Serious complications have also been reported with the prostaglandins used in association with RU-486. These complications include severe low blood pressure, heart attacks, and deaths. Because no new drug application has been submitted to FDA for review, the agency has not made a

Prepared by: _____ :HF-40:FDA: __:8/13/92: _____

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OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HF-40		8-13	FDA		8-13			
OC		8-13	HHS		8-13			

FILE

MIF 003664

determination on whether existing safety and effectiveness data would satisfy the statutory criteria for approval for use in the United States.

IMPORT ALERT

In June 1989, FDA issued an import alert on RU-486. A short summary may be helpful to clarify FDA's import policy. Under the Federal Food, Drug, and Cosmetic Act, an unapproved new drug may not be legally imported into the United States except under an investigational new drug application. However, FDA has for many years exercised its enforcement discretion to not prevent the importation of small amounts of drugs and other products for personal use, provided products are not commercialized or promoted. In the absence of commercialization or promotion, under FDA's policy on personal use importations, if the use is not for treating a serious condition and the product is not known to represent a significant health risk, importation might be allowed. If the intended use is for a serious condition, then additional factors are considered in exercising the agency's enforcement discretion. Importation might be allowed when the intended use is (1) for a serious condition for which effective treatment may not be available in the United States, (2) the product does not represent an unreasonable risk, and (3) the individual affirms in writing that the drug is for personal use and identifies the U.S. doctor responsible for treatment or provides evidence that the drug is for continuation of treatment begun in a foreign country.

After questions had been raised concerning whether RU-486 could be imported under the agency's personal use importation policy, FDA in 1989 issued an import alert stating 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, revised in 1990, remains the current guidance to FDA employees.

RECENT LITIGATION

With a great deal of media attention, on July 1, FDA and the Customs Service detained a small quantity of RU-486 from a woman entering the United States at Kennedy Airport in New York. The agency and the press had been alerted that Ms. Leona Benten would be carrying RU-486 on her person when she arrived in the United States. On July 7, three plaintiffs--Ms. Benten, her physician, and the person who assisted them in obtaining the drug--filed a class action lawsuit on behalf of all women who want to import the drug for personal use as an abortifacient under the supervision of a physician.

On July 14, the District Court issued an order directing FDA to release the drug to plaintiffs. In granting the preliminary

injunction, the District Court ruled that Ms. Benten would suffer irreparable injury if she could not terminate her pregnancy through use of the drug rather than through surgical abortion. The court also ruled that FDA's import alert instructing agency officials to detain the unapproved drug was promulgated without notice and comment rulemaking, in violation of the Administrative Procedure Act and FDA regulations. In addition, the court found that FDA's action was an "arbitrary and capricious" change from the Agency's policy permitting importation of some drugs for personal use.

Upon the government's motion filed within hours of the District Court's decision, the Court of Appeals stayed the order that had directed FDA to release the drug. On July 15, plaintiffs requested the Supreme Court to vacate the stay. In refusing plaintiffs' request, the Supreme Court concluded that plaintiffs had failed to demonstrate a substantial likelihood of success on the merits of their claim that rulemaking was required. The Court's majority also concluded that the allegations of constitutional rights violations were not properly before them because those issues had not been raised in the lower courts. Justice Stevens, however, dissented, concluding that an undue burden had been imposed on the exercise of constitutionally protected abortion rights. Justice Blackman dissented without opinion.

The appeal of the preliminary injunction order may now be moot, because Ms. Benten has had a surgical abortion. The government intends to ask the Court of Appeals to dismiss the appeal and vacate the existing order. The government must respond to the original complaint, which requests the District Court to declare the import alert to be illegal, in early September. The District Court is also currently considering the motion of Mr. A. Lawrence Washburn, Jr., to intervene in the litigation to be appointed guardian of the unborn fetuses of pregnant women seeking to import RU-486.

RESEARCH

FDA's import alert on RU-486 is not designed to, and does not, thwart appropriate research or clinical trials with the drug. The import restrictions do not prevent importation of RU-486 for any experimental use if an approved Investigational New Drug (IND) Application exists. Roussel Uclaf is currently providing the drug for trials under approved INDs, but has indicated that it will not provide the drug for United States studies of the abortifacient use.

A list of the INDs in effect as of July 24, 1992, is attached. There is currently no active IND for abortifacient use. As you can see, RU-486 is under study in this country for a variety of indications

[redacted]

JULY 1992 CONGRESSIONAL HEARING

Representative Wyden's House Small Business Subcommittee on Regulation, Business Opportunities and Energy conducted a hearing on RU-486 on July 28 at which the actress Cybill Shepherd, among others, urged Congress to allow importation of the drug. FDA did not testify. [redacted] who has a brain meningioma, testified about his and his physician's attempts to acquire RU-486 from Roussel Uclaf to treat his condition under a single-patient IND. He testified (incorrectly) that FDA's import "ban" on RU-486 jeopardizes his chances to survive and that red tape has thwarted his efforts. However, he also testified that the company was not willing to release the drug to him.

[redacted]

LETTER FROM REPRESENTATIVE WYDEN

You should be aware that Representative Wyden wrote to Dr. Bruce Chabner of the National Cancer Institute, on August 10, 1992, to request information about NCI's interest in pursuing studies on RU-486 and breast cancer, [redacted]

As is apparent, there has been much public attention focused on RU-486 lately. However, there has been no change in its regulatory or marketing status in this country. There are no new drug applications for the commercial marketing of RU-486 in this country for any indication, and FDA remains willing to review applications for investigation or marketing in the U.S. of RU-486. I will keep you informed of any developments on the status of this issue.

/s/

Attachment

APPEARS THIS WAY
ON ORIGINAL

RON WYDEN, OREGON
CHAIRMAN

AND E. NEAL, MASSACHUSETTS
W. H. FLAKE, NEW YORK
ERT E. ANDREWS, NEW JERSEY
ARTIN LANCASTER, NORTH CAROLINA
ASTOR, ARIZONA

102d Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Energy
B-363 Rayburn House Office Building
Washington, DC 20515-6318

MINORITY MEMBERS
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STEVE JENNING
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202-225-7797

GRAYSON J. FOWLER
SUBCOMMITTEE COUNSEL

JENNIFER LOON
MINORITY SUBCOMMITTEE PROFESSIONAL
STAFF MEMBER
202-225-3605

July 22, 1992

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

Dear Dr. Kessler:

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

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

-- A brief description of those trials, individually.

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

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

As I believe this information is readily available, and may have been recently collated and up-dated by your staff, I request that your response be telefaxed to my subcommittee staff by close-of-business, Thursday. Their number is (202) 225-8950.

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

Thank you for your assistance in this matter.

Sincerely,

RON WYDEN
Chairman

FF 10289
issued 7/24

MIF 003669

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

December 14, 1992

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

Dear Dr. Sakiz:

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

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

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

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

AF
9208093

MIF 003670

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, December 17, 1992

DEC 17 11 56 AM '92

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

Dear Doctor Kessler,

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

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

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

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

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

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

Yours sincerely,

9208252

35, Boulevard des Invalides 75007 Paris

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

FEB 5 1993

TO: Commissioner of Food and Drugs

FROM: Acting Assistant Secretary for Health

SUBJECT: Importation of RU-486

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

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

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

/S/

Attachments

APPEARS THIS WAY
ON ORIGINAL

9300540

THE WHITE HOUSE

WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

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

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

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

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

William J. Clinton

APPEARS THIS WAY
ON ORIGINAL

MIF 003673

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

FEB 1 1993

TO: The Acting Assistant Secretary for Health

FROM: The Secretary

SUBJECT: Importation of RU-486

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

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

Donna E. Shalala

Attachment

APPEARS THIS WAY
ON ORIGINAL

MIF 003674

Memorandum

March 30, 1993

Note to [redacted]

Subject: Letters from Potential Investigators for RU-486 Research

Sol,

We received the attached note from [redacted] on the letter from [redacted] (TRAC 9301482). Could you please draft an appropriate response to [redacted] and give it to me so that we can clear it with [redacted]. The cleared draft response can then be used for other investigators who write in. Thanks.

/S/

[redacted]
Senior Policy Analyst

Attachment

APPEARS THIS WAY
ON ORIGINAL

9301482

[redacted] Family & Community Medicine

[redacted]

March 19, 1993

David Kessler, MD. PhD
Director
US Food and Drug Administration
Rockville, MD 20857

RE: Our Interest in Serving as Investigators for RU-486 Research

Dear Dr. Kessler:

I am writing to inform you that if and when RU-486 becomes available as an investigative drug in the U.S., I will be interested in serving as an investigator for research on this pharmaceutical agent.

We have sufficient numbers of patients to conduct investigations of this drug. We operate a busy academic family practice clinic ([redacted] visit per year) in which a major portion of the patient population consists of women of childbearing age. In fact, the most frequent reason for a visit to our clinic is pregnancy care.

Our clinical facility and patient population regularly participates in research activities. My department, which has one of the largest research programs of any department [redacted] has conducted numerous large-scale pharmaceutical research projects. I have personally served as an investigator for several drug studies.

I have had a long-standing interest in the development and clinical use of RU-486, and have published on the topic. My CV is enclosed. I hope that you will make our interest in this research known to the appropriate individuals.

Sincerely,

[redacted]

Professor

cc: [redacted]
Department Head

[redacted]

9301482

ISSUE MANAGEMENT: RU-486

Summary of Initiative - On January 22, 1993, President Clinton issued a memorandum directing Secretary Shalala to assess initiatives to promote the testing, licensing, and manufacturing in the United States of RU-486 (mifepristone) and to direct the Food and Drug Administration (FDA) to reassess whether RU-486 qualifies for importation under FDA's personal use importation policy.

Measure of Success - The end result that would constitute success for this initiative would be the submission of a New Drug Application (NDA) to FDA for RU-486 for abortifacient use.

Strategic Plan - RU-486 is manufactured by the French firm Roussel-Uclaf and approved to help induce abortions in France, the United Kingdom, and Sweden. Roussel-Uclaf has stated that it can act in the U.S. only with the approval of its parent company, Hoechst AG. Hoechst has historically refused to permit Roussel-Uclaf to seek marketing approval for RU-486 as an abortifacient in the U.S.

In June 1989, after questions had been raised concerning whether RU-486 could 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 Customs Service detained a small quantity of RU-486 from a woman entering the U.S. at Kennedy Airport in New York. The woman and two other individuals filed a lawsuit which is still being litigated. In accordance with the President's January 22 memorandum, FDA is reassessing whether RU-486 might qualify for importation under FDA's personal use importation policy and whether the import alert should be rescinded.

On December 16, 1992, 34 newly elected House members urged Hoechst AG to begin studies of the abortifacient use in the U.S., stating that "American women should have the same choice as women in other nations to terminate a pregnancy in a safe and responsible manner." Other members of Congress have also written to Roussel-Uclaf urging them to submit a marketing application for RU-486. In December, Commissioner Kessler wrote to Roussel-Uclaf on this drug. In response, on December 17, 1992, Roussel-Uclaf informed FDA that it was reviewing its strategy for beginning clinical trials in the U.S.

In February 1993, senior Roussel-Uclaf representatives met with Commissioner Kessler and some key FDA staff to discuss the availability of RU-486 in the U.S. for marketing and research, focusing on the types of data FDA would need in considering an NDA for RU-486. While asserting RU-486 should be made available in the U.S., the firm emphasized Hoechst's mandate that Roussel-Uclaf find a way to achieve the goal without the involvement of Roussel-Uclaf. Possible avenues discussed were a U.S. pharmaceutical firm, a research center, or a university. In March, the Secretary wrote to the president of Hoechst and urged him to eliminate the corporate barriers to the introduction of RU-486 into the U.S. market. In

a related development, Searle has recently expressed reluctance to commit its prostaglandin, Cytotec, to be used in conjunction with RU-486.

At a meeting on April 20 with company representatives, Roussel-Uclaf agreed to license the drug and to transfer the technology necessary for producing the drug to the Population Council, a non-profit scientific and technical organization, for distribution in the U.S. The Population Council will locate a manufacturer for RU-486 in this country and plans to begin a U.S. clinical trial involving at least 2,000 women to test the drug. The Population Council will move as soon as possible to submit an NDA to FDA. Once a New Drug Application is submitted for RU-486, FDA will conduct its formal review of the data concerning the safety and efficacy of the drug.

[redacted]

Agency Lead and Coordination - FDA has the lead responsibility for developing this initiative. FDA representatives met with representatives from the National Institutes of Health on March 2, 1993, to discuss initiatives to promote the testing in the U.S. of RU-486 and other antiprogestins.

[redacted]

Key Contacts -

White House Policy:
White House Communications:
White House Legislative:
Agency: [redacted]

APPEARS THIS WAY
ON ORIGINAL

RU486WH.
Based on RU486. Transition Issue Sheet) which was:
Revised 1/4/93
Updated: 3/23/93
Revised it, 3/24/93
Revised: 4/21/93
Revised: 5/19/93
Edit: 5/19/93
Cleared: 5/19/93
Edit: 5/20/93

APPEARS THIS WAY
ON ORIGINAL

IMPORT ALERT

ORO/DFI (HFC-131)
IMPORT OPERATIONS BRANCH

Automatic Detention of Abortifacient Drugs

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

TYPE OF ALERT: Automatic Detention

PRODUCT : Abortifacient Drugs (drugs that induce abortion)

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

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

PAC : 56008H

COUNTRY : All

MANUFACTURER/
SHIPPER : ALL UNAPPROVED

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

RECOMMENDING
OFFICE : HFC-131 Import Operations Branch

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

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

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

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

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

MIF 003680

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

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

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

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

INSTRUCTIONS : Automatically detain all shipments of unapproved abortifacient drugs.

FOI : No purging is required of this alert.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

9-71-00 PURPOSE

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

9-71-10 BACKGROUND

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

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

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

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

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

9-71-20 PERSONAL BAGGAGE

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

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

9-71-25 MAIL SHIPMENTS

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

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

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

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

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

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

9-71-30 GENERAL GUIDANCE

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

A. Commercial or Promotional Shipments

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

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

B. Products Other than Drugs and Devices

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

C. Drugs, Biologics, and Devices

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

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

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

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

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

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

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

9-71-40 IMPORT ALERTS

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

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release January 22, 1993

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

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

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

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

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

WILLIAM J. CLINTON

# # #

MIF 003689

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

April 22, 1994

James S. Boynton, Esq.
Christy & Viener
620 Fifth Avenue
New York New York 10020-2402

Lester S. Hyman, Esq.
Swidler & Berlin, Chartered
3000 K Street, N.W., Suite 300
Washington, D.C. 20007-5116

Dear Mr. Boynton and Mr. Hyman:

As you requested, enclosed are the Agency's preliminary comments on the April 11, 1994, proposed distribution scheme for mifepristone in the United States. As I have mentioned to you, the question as to whether any residency requirement can be imposed needs further examination. Moreover, any final comments on the distribution scheme must follow the Food and Drug Administration's review of the scientific, medical, and other data and information contained in a new drug application for the drug.

We are heartened by the fact that you, Roussel Uclaf, and Hoechst AG are close to agreeing on a distribution plan. As the Secretary noted, however, we expect all issues, not just the distribution issue, to be concluded by May 15, 1994.

As Commissioner Kessler promised in our recent meeting, the Food and Drug Administration stands ready to assist all parties in any scientific, medical, or labeling issues that may arise.

Sincerely yours,

/s/

[ ]

Enclosure

9403641

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 14, 1994

Dr. Andre Ullman
Roussel Uclaf
102, route de Noisy
93235 Romainville Cedex
FRANCE

Dear Dr. Ullman:

The Food and Drug Administration asks that Roussel Uclaf provide The Population Council access to, and the ability to copy and submit to the United States Food and Drug Administration, any information relevant to the use of mifepristone (RU-486) for the termination of early pregnancy. This request includes case report forms, electronic data bases, synthesis and manufacturing information, and any other information required by United States laws and regulations to be included in a New Drug Application for mifepristone.

We would appreciate your prompt consideration of this request.

Sincerely yours,

/s/

APPEARS THIS WAY
ON ORIGINAL

94-8442

MIF 003691

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 3, 1996

NOTE TO [redacted] OLA

Subject: Additional Records for Document Request on RU-486 from Representative Coburn--TRANSMITTAL

Per discussions involving [redacted] Executive Secretariat, [redacted] and other OLA staff, we again searched our records for further documents (general correspondence) that OLA believes is responsive to this Congressional document request. We have found the attached records, which we believe meet OLA criteria. These materials have been redacted for patient identifiers and are submitted in FOI-releasable form. This set of records supplements our earlier submission of November 30, 1995, which was provided under a cover note to [redacted] of your office.

Our search also disclosed the existence of several letters, written in 1995, commenting on a Citizen Petition, subumitted by Americans United for Life , concerning RU-486 (95P-0054). If you intend to provide these letters you will need to get them from Dockets Management.

I have also taken the liberty of preparing an index (copy enclosed) for the attached documents.

This list is provided to you for ease in determining what documents we are forwarding.

If you have any questions concerning these documents, you may contact me at [redacted] or [redacted] and [redacted]

/S/

[redacted]

FDA Executive Secretariat

Attachments

cc: [redacted]

APPEARS THIS WAY
ON ORIGINAL

American Public Health Association

1015 Fifteenth Street, NW
Washington, DC 20005
202/789-3660

Mervyn Susser, MB, BCh.
FRCP(E), DPH
Editor, American Journal of Public Health

June 9, 1992

Commissioner David Kessler, MD, PhD
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

I shall be gratified if you find it possible to respond to my request for a brief exposition of the FDA position on RU 486 in relation to (a) its use in investigations and research into all uses, particularly as a means of intercepting unwanted pregnancies and (b) the marketing of the drug, again with attention to all its uses, including particularly the interception of unwanted pregnancy.

Such a paper would best take the form of a Commentary (up to 2500 words or fewer, see enclosure for authors) in the context of the enclosed article on RU 486, which will appear in our October issue. The deadline is July 10.

I very much hope you will write this piece, which will surely be an important part of the dialogue on this public health issue.

Sincerely,

Mervyn Susser

Enclosures

APPEARS THIS WAY
ON ORIGINAL

9204775

MIF 003693

What *AJPH* Authors Should Know

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Length. Conciseness earns points. Our preference for Articles and Commentaries is no more than 4500 words and for Briefs no more than 1000 words (excluding references, tables, and figures). For Letters to the Editor we try to keep to 400 words.

Special departments. Four of these, listed below, invite contributions that go directly to the appropriate Contributing Editor. Authors should follow the format found in previous Journal issues.

Notes from the Field describes field and teaching experiences of more than local interest.

Public Health Then and Now is devoted to history that bears on contemporary public health.

Health Law and Ethics deals with the common ground as well as conflicts between public health, law, and ethics.

Policy Forum publishes papers on topics of current or future import for public health.

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Authorship. We feel that authorship is depreciated by a multitude. More than six authors will need justification. We recommend the criteria suggested by the International Committee of Medical Journal Editors (*N Engl J Med.* 1991;324:424-428) and ask for assurances on this score.

Format. The Journal generally follows the guidelines of the International Committee (as above) and the *American Medical Association Manual of Style* (8th ed. Baltimore, Md: Williams & Wilkins; 1989).

Type everything double-spaced on one side of a sheet of 8-1/2 x 11-inch paper, with 1-inch margins on all sides. Assemble your material in the order discussed below.

Cover letter. This letter is signed by all authors. One should be named correspondent (with address, telephone and fax numbers). We require two statements, one that all authors have participated in three activities (1. conception/design or analysis/interpretation; 2. writing; 3. approval of final version) and can take public responsibility for the content of the paper, and another that the material has neither been published nor is being considered elsewhere. Also, possible conflicts of interest, e.g., financial arrangements in relation to products studied, should be disclosed. (Whether and how such information is published is discussed between authors and Editor if the paper is accepted.)

The Editors will find helpful a brief indication of your sense of the main interest of the paper to the readers of *AJPH*. You may suggest up to three reviewers whom you believe to be knowledgeable about its subject. Finally, you should mention supplementary unpublished material enclosed to support your results as well as overlapping material already published.

First title page. Include 1. main title; 2. "running head" of up to 45 characters; 3. names of all authors (full first names), degrees and institutional affiliations at the time of the work; 4. name and address for (a) correspondence and (b) reprint requests; 5. number of words in text and number of tables, figures, if any; and 6. key words (best chosen from *National Library of Medicine. Medical Subject Headings—Annotated Alphabetical List 1992*. Bethesda, Md: National Institutes of Health; 1991).

Second title page. This page gives only the title of the paper so that reviewers can be kept blind to authorship as far as possible. We appreciate authors' removing anything that obviously indicates identity from the rest of the paper as well.

Abstract. For Articles, limit the abstract to 180 words set out under four heads: *Objectives* (hypotheses etc.); *Methods* (design, population, analysis); *Results; Conclusions*. For Briefs, which are unstructured, the limit is 100 words.

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Many published references are in error. Verify references in the original or, second best, cite the secondary source. For these and for direct quotations give page numbers. List only references accessible to readers. Cite personal communications with source and date in text only.

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Footnotes. These are discouraged except in tables.

Tables and figures. Arrange each on a separate sheet with a title as a self-contained unit. Figures should be professionally drawn or prepared on a computer and laser printed, with a separate sheet giving legends.

Supplementary material. Two copies of work important to the paper, published or unpublished, should accompany the submission.

Number of copies. Please send five copies of the paper, complete with all components intended for publication.

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Manuscripts are acknowledged upon receipt. We aim to sustain or better our average of 3 months between receipt and decision to publish and 6 months between acceptance and publication.

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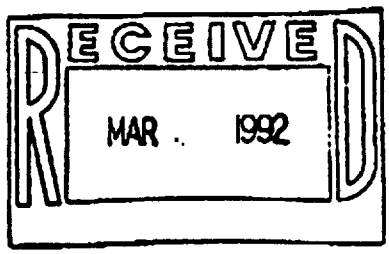

RU 486 AND THE LAW OF ABORTION

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APPEARS THIS WAY
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RU 486 and the Law of Abortion

Suzanna S. Banwell, J.D., M.P.H.* and John M. Paxman, J.D.**

RU 486 (mifepristone), a steroid analogue able to induce menses within ten weeks of the last menstrual period[1] was approved for use in conjunction with a prostaglandin in France in September 1988, and by early 1991 more than 60,000 French women had used it.[2] The approval and use of RU 486 (marketed in France by Roussel Uclaf under the trade name "Mifegyne") and prostaglandin therapy (RU 486/PG) in France was controversial, illustrating how politics as well as law can influence the availability of reproductive technology. (One month after introducing RU 486, Roussel Uclaf suspended its distribution citing boycott threats primarily from U.S. anti-abortion activists. Two days later the French government, which owns 36 percent of Roussel Uclaf, ordered the manufacturer to resume distribution of RU 486 in France. Health Minister Claude Evin called RU 486 "the moral property of women." Among others, representatives of the Catholic Church reacted sharply to the government's order.[3])

RU 486/PG has been roundly praised as the answer to the abortion debate by proponents of a woman's right of choice in matters of reproductive health, and inveighed against as the "death pill" by opponents of legal abortion. Both high praise and condemnation obscure some of the basic facts about RU 486/PG, and cloud its already uncertain legal status. In this paper we will attempt to distill the essence from the fact, fiction and impressions of the debate. Our aim is to determine how RU 486/PG will be received by various abortion legislation world wide. The politics of the matter aside, we take the view that much of the confusion surrounding RU 486/PG arises because of the vague, medically-imprecise language often used in legislation to describe events that are part of the reproductive process. Here we assess the reception RU 486/PG is likely to encounter under current legislation, and ultimately suggest ways the law might be interpreted or amended to more appropriately accommodate advances in reproductive medicine. The framework for our analysis builds on the one developed by Lee and Paxman to describe the legal effect of the introduction in the mid-1970s of menstrual regulation techniques.[4] Finally, we call into question the appropriateness of involving the criminal law in areas of reproductive health at all.

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The Reproductive Process and RU 486

Implantation of the fertilized ovum in the uterus begins about six days after conception and takes 6-8 more days to complete.[5] When administered within 8 weeks from the woman's last menstrual period (LMP), RU 486 blocks or inhibits the progesterone receptor sites in the uterine lining depriving them of the progesterone necessary for successful implantation. The "antiprogestin" RU 486 has a greater affinity for the progesterone receptor sites than progesterone itself,[1] and without progesterone menses occurs.[6] The recommended 600 milligram oral dose of RU 486,[7] used alone, is 60-85% effective in inducing menses and in terminating very early pregnancies. (Clinical tests of much lower doses are ongoing.)[8] When prostaglandin, a naturally occurring hormone which can induce uterine contractions, is administered by injection or vaginal suppository 36-48 hours after the RU 486, the effectiveness is 95-100%[7 9] comparing favorably to the 97-99% success rate of the oral contraceptive pill in preventing pregnancy.[10] The bleeding that occurs as a result of RU 486/PG use is like that of a heavy menstrual period or an early surgical abortion,[11] though blood loss after treatment increases with gestational age, an important reason why RU 486/PG is only recommended for use before the 56th day of amenhorea.[11]

RU 486/PG is generally considered to have limited side effects, including nausea, abdominal cramping, and, rarely, heavy bleeding requiring blood transfusions. However, there has been one death in France attributed to the use of prostaglandins in conjunction with RU 486. A 31 year old woman, a heavy smoker with 11 children, suffered a heart attack after an injection of synthetic prostaglandin. Now the dosage of prostaglandin has been reduced by 50% in France, and smoking and age greater than 35 are considered risk factors for the treatment.[2] Testing to date has not determined the effects on the fetus should the procedure fail and pregnancy become established, but RU 486 has been shown in clinical studies to cross the placenta.[12] Therefore, women in France are required to agree to a surgical abortion should RU 486/PG therapy fail. For all of the forgoing reasons, medical experts recommend the use of RU 486/PG be closely medically supervised.[11 13 14]

Although the French have approved RU 486/PG only as an abortifacient, it is thought to have numerous other potential applications. For instance, it may be useful in softening and dilating the cervix to aid difficult deliveries, though "extreme caution" is recommended due to uncertainty regarding fetal toxicity,[1] and to ease the delivery of stillbirths and aid later surgical abortions.[12 15] RU 486 may also prove effective in treating certain causes of infertility such as endometriosis.[16] It has also shown promise as a once a month "menses inducer" and as post-coital "morning after pill", and the study of the contraceptive properties of RU 486 as an ovulation inhibitor is presently underway.[17 18] RU 486 may also have non-reproductive applications in treatment of breast cancer, hormone dependent and certain other tumors, Cushing's Syndrome, glaucoma, skin burns and abrasions.[17]

Although access to RU 486/PG under the framework of abortion legislation is now ensured in France, its distribution is being tightly controlled. Roussel Uclaf is, apparently, making the drug available for research and use overseas only in response to direct, official requests to the World Health Organization (WHO) from foreign governments. (Under the sponsorship of the WHO, RU 486 has been clinically tested in several countries including Sweden, the Netherlands, Hungary, Great Britain, Italy, India, Chile, Hong Kong, and Singapore.[18] The Population Council has also tested it in the United States.[19]) Some observers have maintained that, should legal access to RU 486 remain as restricted as it is, the likelihood that it will proliferate on black markets is high.[20] The desire to have access to a drug like RU 486 that inhibits or interrupts pregnancy is universal. Indeed, a prostaglandin, misoprostal, whose principal use is to treat peptic ulcers but whose properties will induce a miscarriage, is available on the market in Brazil through G.D. Searle under the trade name Cytotec. Abortion is basically illegal in Brazil, but the abortion rate is one of the highest in the world, and there is increasing evidence that Cytotec is being utilized by women to commence abortion.[21]

RU 486/PG and the Law

Whether RU 486/PG will be made legally available around the world will depend not only on politics, but also on the nature and interpretation of the various abortion laws in force. The definition of key terms within some of those laws may become pivotal. Terms often used in

abortion legislation but seldom clearly defined include "pregnant," "with child," "abortion," and "miscarriage." Statutory language often uses such terms in a way that makes interpretation near impossible. Yet the definition of these terms is important if we are to know whether the law will accommodate or bar the use of RU 486/PG and other advanced reproductive technologies. If abortion is defined to include techniques that operate before implantation is complete, RU 486/PG will be regulated by abortion law. If not, RU 486/PG could be considered a contraceptive and be made more widely available. This distinction is particularly important as abortion legislation generally imposes criminal penalties.

RU 486/PG and Liberal Abortion Laws

In France, RU 486/PG is regarded as an abortifacient and its use is subject to the provisions of French abortion legislation. Legislation like France's occupy the liberal end of the spectrum of abortion laws. They permit the legal termination of pregnancy, usually during the first trimester, for a variety of reasons ranging from personal choice to social and medical indications. Approximately 63% of the world's population live within countries that have liberal abortion laws.[22] Under these laws, the pattern may well be that, as has happened in France, RU 486/PG is treated as an abortifacient and its uses will be subject to the rules and regulations that govern abortion procedures in general. In these countries we anticipate that politics will play a larger role in determining access to RU 486/PG then legal restrictions on abortion will. Access to RU 486/PG might also be limited in some of these countries due to lack of medical infrastructure and reluctance, therefor, on behalf of Roussel Uclaf to distribute RU 486 there.

Some jurisdictions have explicitly adopted a definition of pregnancy that would seem to bar any legal challenge to the introduction and use of RU 486/PG. Germany, New Zealand, and Liberia have adopted the medical definition of pregnancy[23] for use in their abortion statutes, i.e. that pregnancy begins after completion of implantation.[24] Statutes that use this medical definition of pregnancy regard menses inducing techniques used prior to implantation as contraception. Others recognize some of the subtleties introduced by medical advancement in the area of in vitro fertilization. For example, the British Health Minister in 1981, Dr. Gerard Vaughn, declared that

mere fertilization did not create a pregnancy (petri dishes cannot get pregnant), and therefore implantation must occur before there is a pregnancy. Following Vaughn's lead, the English Attorney General, Sir Michael Havers, opined that attempts to prevent implantation are neither governed nor restricted by abortion law.[25] Indeed, RU 486/PG has been approved for use in Great Britain. In the United States, the Model Penal Code, which has been cited in decisions of the U.S. Supreme Court, states:

> Nothing in the Section shall be deemed applicable to the prescription, administration or distribution of drugs or other substances for avoiding pregnancy, whether by preventing implantation of a fertilized ovum or by any other method that operates before, at, or immediately after fertilization.[26]

Accordingly, RU 486/PG would not be considered an "abortifacient" in the U.S. if administered after fertilization but prior to the completion of the implantation of a fertilized ovum.

RU 486/PG and Restrictive Abortion Laws

In countries where abortion law is more restrictive, the introduction of RU 486 may encounter a number of legal barriers. Here, statutory language definition and interpretation become critical. On the one hand, if pregnancy is legally defined as beginning after implantation is complete, early use of RU 486/PG would not be regarded as the termination of a pregnancy, and therefore could probably be employed without implicating criminal abortion law. Once implantation was completed, however, the use of RU 486/PG would be considered abortion and would require compliance with abortion law. On the other hand, if pregnancy is deemed to begin with fertilization, even very early use of RU 486 might not be permitted under the terms of abortion law. The meaning of "pregnancy," then, may be pivotal. This situation raises a host of difficult questions for medical practitioners and jurists alike.

For example, the earliest that the most accurate pregnancy tests, radioimmunoassay pregnancy tests, can detect HCG (the hormone detected by pregnancy tests) in significant levels is 6-8 days after fertilization, or about a week before the next expected menstrual period.[10] These tests must, however, be performed in laboratories, because they require the use of radiolabeled material and sophisticated equipment.[27] Except for radioimmunoassay tests, virtually all other pregnancy tests are only accurate 4-14 days after a missed menses (depending on the