exchange of information be conducted in an atmosphere of mutual trust and cooperation. We hope you will honor our request to preserve the confidentiality of this type of information when it is transmitted to the Subcommittee in the future. If there is any uncertainty about whether particular information should be kept confidential, we encourage and expect consultation with you or your staff in advance of any public release of the information. Please notify me immediately if this understanding is unsatisfactory in any way.

I appreciate your continued cooperation in addressing this matter.

Sincerely yours,

Carol R. Scheman
Deputy Commissioner
for External Affairs

Enclosures

R/D: 7/29/92
Edited: GCF-1:8/4/92
Edited: GCF-1:8/4/92
Edited: HF-1:8/4/92
Edited: HFW-1:8/5/92

cc: HF-24
HFW-1
HFW-10
GCF-1

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

File: RU 486

Memorandum

Date January 6, 1992

From [redacted] Legislative Affairs (HFW-1)

Subject Summary of Hearing - December 5, 1991, "The Safety and Effectiveness of the Abortificient, RU-486, in Foreign Markets; Opportunities and Obstacles to U.S. Commercialization," before the House Small Business Subcommittee on Regulation, Business Opportunities, and Energy

To Policy Board

A member of my staff monitored the above-mentioned hearing. I am attaching a copy of her report for your information. If you desire copies of the available attachments to this report, please contact [redacted] of my staff on

[/S/]

Attachment

cc: [redacted]

APPEARS THIS WAY
ON ORIGINAL

MIF 002702

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date . January 2, 1992

From Legislative Analyst, HFW-14

Subject December 5, 1991 Hearing before the House Small Business Subcommittee on Regulation, Business Opportunities, and Energy, entitled, "The Safety and Effectiveness of the Abortifacient RU-486 in Foreign Markets; Opportunities and Obstacles to U.S. Commercialization."

To _____ for Legislative Affairs, HFW-1

Through: _____ Legislation and Special Projects, HFW-14 /S/

Representatives Present: Ron Wyden (D-OR), Chairman

Background: This hearing examined the experience in international markets regarding the safety and effectiveness of RU-486, and the barriers involved with the drug's use in the U.S. Representative Wyden placed emphasis on his bill H.R. 875, the "RU-486 Regulatory Fairness Act of 1991." This bill would make the FDA import alert for RU-486 ineffective.

Representative Wyden, in his opening remarks, said that the Subcommittee is examining the French drug RU-486 through clinical experience as an abortifacient, results of medical research with the drug in the treatment of other illnesses, and the use of the drug as a new contraceptive. He emphasized that the drug is not available in the U.S. because "the manufacturer sees too many political, legal and commercial obstacles in its path." He indicated that American researchers have told the Subcommittee that they are reluctant to work with drugs which may have abortifacient properties because they fear they "won't meet the political litmus test driving some Federal policy makers." According to FDA there have been two compassionate use approvals, and no IND applications in at least 3 years for RU-486 basic research. The Subcommittee finds that since the FDA issued its import alert on RU-486 in 1989 medical research with RU-486 in the U.S. has come to a standstill.

Panel 1: Dr. Etienne-Emile Baulieu, Professor, Department de Chimie Biologique, INSERM, Paris, France;

Dr. Annie Bureau-Roger, OB-GYN Clinician, Hospital Broussais, Paris, France;

Mrs. Dilys Cossey, Chairwoman, British Family Planning Association, London, England;

Dr. Beverly Winikoff, Senior Medical Advisor, The Population Council, New York, New York;

Dr. Baulieu, the discoverer of RU-486, explained that the drug has anti-steroid hormone properties and is synthesized by the Roussel-Uclaf Company, Paris, France, which owns a world-wide patent for all uses. Approximately 100,000 women have used the drug for voluntary pregnancy interruption in France which involves four medical visits. The process, based on clinical experience, is 95 percent effective and has been determined to be safe. The drug should be administered under medical supervision, rather than over-the-counter because pregnancy itself can be a risk requiring medical attention. The drug can be used for other medical indications such as endometriosis, fibroids, breast cancers, Cushing's syndrome, and meningioma. The drug can also be used for the repair of wounds or burns and some aspects of stress, he added.

Dr. Bureau-Roger discussed the results of a large RU-486 trial by Roussel Laboratories from May 1988 to September 1989 involving approximately 16,000 women. The success rate of the trial was 95.3 percent (defined as interruption of the pregnancy and complete expulsion). Two point eight percent experienced incomplete expulsion, 1.1 percent required surgical termination, and .8 percent required a hemostatic procedure (arrest of bleeding). The trial involved the administration of RU-486 and, two days later, a low dose of prostaglandin analogue (PG), hormones naturally involved in contractions of the uterus which hasten expulsion and make RU-486 more efficient. Serious cardiovascular side effects after the administration of PG were reported in 4 women: 1 myocardial infarction and 3 serious hypotension incidents. Recovery was complete in all 4 cases. Since the introduction of the drug and its use in more than 60,000 women, 2 other myocardial infarctions have occurred after PG injection, one of which was fatal.

Ms. Cossey testified on behalf of the European Family Planning Association as a representative of the International Planned Parenthood Federation. She described herself as a pro-choice campaigner committed to the availability of safe, legal abortion for unwillingly pregnant women. She recognizes RU-486 as a choice in abortion techniques for women who wish to terminate their pregnancies. The drug is only available in Britain under the terms of the 1967 Abortion Act, requiring permission from 2 physicians and a signed certificate of need. RU-486 may be taken in the first 63 days of pregnancy (in France it is limited to the first 49 days). She stated that "It is a matter of regret that the way forward in countries like the United States appears to be blocked by ignorance and fear prohibiting RU-486 for research work in areas other than

abortion." She also indicated that India and China are interested in the drug.

Dr. Winikoff stated that there is great concern over the rate of maternal death in the world today. "The latest estimate is over 500,000 women's lives lost to causes related to pregnancy every year - most in developing countries and most entirely preventable." The largest single cause is poorly performed abortions. Research in India and Cuba about women's reactions to medical and surgical abortions has indicated that more than 90 percent of the first 67 women to use RU-486 were highly satisfied or satisfied, and only 9 percent were unsatisfied, she said. Medical abortifacients have been considered a potentially more accessible and safer technology that could reduce medical resources and surgeon hours, and be largely free of the complications associated with surgical procedures.

Representative Wyden stated that he was pleased that Dr. Baulieu and Dr. Bureau-Roger both support additional trials in the U.S. on RU-486. He explained that he had introduced a bill that would lift the import alert and hoped that would help encourage research with the drug.

Representative Wyden asked what are the obstacles that prevented the U.S. from being chosen to conduct the large scale breast cancer trial with RU-486 that was awarded to Canada by Roussel-Uclaf. Dr. Baulieu responded that many people are encouraged by the success of the drug, but the success is also creating a tense and difficult environment within the U.S which could have contributed to the decision not to award the trial to the U.S.

Panel 2: Dr. Gary Hodgen, OB-GYN Researcher, East Virginia Medical School, Norfolk, Virginia;

Dr. David Grimes, OB-GYN Researcher, School of Medicine, University of Southern California, Los Angeles, California;

Dr. David Baird, OB-GYN Researcher, Edinburgh University, Edinburgh, Scotland;

Dr. Marc Bygdeman, OB-GYN Researchers, Karolinska Hospital, Stockholm, Sweden.

Dr. Hodgen previously worked for 15 years at NIH in the Pregnancy Research Branch of the National Institute of Child Health and Human Development. He had the occasion to work with Dr. Baulieu doing experiments on RU-486. He indicated that RU486 as well as other abortifacients are useful in clinical practice to: prevent conception; assist in labor and delivery or hysteroscopic procedures; reduce the effects of Cushing's

syndrome; control endometriosis; shrink uterine fibroids; suppress certain estrogen dependent cancer cells; and accelerate breast milk production. He has written more than 30 scientific articles on RU-486 and 5 other antiprogestin medicines. He recommends rescission of the FDA import alert and careful examination of safety and efficacy data on any clinical indications of RU-486.

Dr. Grimes previously worked with CDC as the principal official for evaluating the health effects of abortion in the U.S. He explained the potential for various applications of RU-486. The drug has become an orphan drug in the U.S., not because of unprofitability but by politics, he said. He described an analogy to the drug methotrexate used in cancer chemotherapy which can also induce abortions. "What would have happened had anti-abortion activists persuaded its manufacturer not to market in the U.S. merely because they disagreed with one potential use for the drug?" he added.

Dr. Baird stated that RU-486 in combination with PG is a safe and effective medical alternative to surgical abortion in early pregnancy, as witnessed in extensive trials in over 20 countries. Research has demonstrated that the drugs are likely to have many therapeutic uses in addition to inducing abortions, he added. Unless antigestogens are licensed for use as abortifacients it will not be possible to develop other therapeutic uses and women will be deprived of treatment which would be of great benefit to their health.

Dr. Bygdeman indicated that research on RU-486 has been on-going in Sweden since 1983. The overall Swedish experience is that the method is highly effective in terminating early pregnancy. The frequency of complete abortion varies between 95 and 100 percent. At present, RU-486 is not registered in Sweden or any other Scandinavian country but the manufacturer, Roussel-Uclaf has been petitioned to introduce the drug in Sweden by the Swedish Drug Regulatory Authorities as well as by OB-GYN professors.

Representative Wyden stated that the FDA unquestionably has the authority to issue an import alert on the drug but only uses authority in the case of unsafe drugs, and black market drugs. He asked if panelists were concerned about the import alert. Dr. Hodgen indicated that the alert appears to be in direct conflict with the intention of the FDA to not inhibit research into RU-486.

Representative Wyden asked the panelists about experiences with cardiovascular complications. Dr. Bygdeman said that none had been experienced in Sweden. Dr. Baird indicated that the experience in Britain was similar to that in France.

Panel 3: Mr. Roderick L. MacKenzie, President, GynoPharma, Inc., Somerville, New Jersey;

Dr. Jacqueline Forrest, Social Demographer, The Guttmacher Institute, New York, New York; (No written statement)

Mr. Richard Glasow, Education Director, National Right to Life Committee, Washington, D.C.;

Ms. Eleanor Smeal, The Feminist Majority Foundation, Boston, Massachusetts;

Absent: Dr. Janice G. Raymond, Medical Ethicist, Department of Women's Studies, University of Massachusetts, Amherst, Massachusetts.

Mr. MacKenzie stated that in the U.S. there is a crisis in contraception. The U.S. has one of the highest abortion rates in the developed world because highly effective methods of contraception, such as the IUD or hormones, are used at a much lower rate than in Western Europe. He is concerned that there are too few companies doing any significant contraceptive research. He suggested that the real controversy in this area is the issue of abortion, not product liability.

Dr. Forrest pointed out potential problems associated with the use of RU-486 as an abortifacient. Obstacles of cost, time, and availability are evident due to the necessity for several visits to complete the process using RU-486. The use of the drug would not obviate the need for surgical methods of abortion for these same reasons, and because a backup method must be available for failed medical procedures. She recommends that RU-486 be further studied in the U.S.

Dr. Glasow stated that FDA's import ban has not stopped research on RU-486 for non-abortion purposes, rather it has been going on for a number of years. The National Right to Life Association does not oppose the use of RU-486 for non-abortion purposes.

Ms. Smeal stated it is unconscionable that the U.S. is not conducting trials on RU-486 for breast cancer. She is dismayed that there are women who are being denied hope because of the political climate. She added that women should have access to new methods of contraception and abortion because an unwanted pregnancy is unsafe.

Representative Wyden asked Mr. MacKenzie what it would take for a small company to go forward in the U.S. with RU-486 in the

present climate. Mr. MacKenzie replied that first the manufacturer of the drug, Roussel-Uclaf, would have to make the drug available in the U.S. Until that happens it's a pie in the sky dream.

Representative Wyden asked Dr. Forrest if it is her perception that young doctors are reluctant to enter the field of contraceptive research. She replied that they are concerned with the payoff, getting promoted, and tenure, and concerned about securing research funds.

Representative Wyden asked Mr. Glasow if he supported more research and testing with RU-486. He responded that they do not oppose testing for non-abortion purposes.

Representative Wyden wanted to know what evidence there is that research with RU-486 is flourishing. He added that there have been 2 compassionate use approvals and no applications for INDs in the last 3 years. Mr. Glasow replied that research never ceased and that currently there are three tests ongoing at NIH. Representative Wyden said he would confirm this with NIH.

Ms. Smeal added that research is going on but that it is greatly slowed, and the anti-abortion movement is partially responsible.

Representative Wyden thanked the participants for testifying at the hearing.

Attachments:
Witness List
Testimony of Witnesses

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

RUTH MERKATZ, PH.D., R.N.

SPECIAL ASSISTANT TO THE COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES, AND ENERGY

COMMITTEE ON SMALL BUSINESS

HOUSE OF REPRESENTATIVES

IN

CAMDEN, NEW JERSEY

MAY 8, 1992

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I am Dr. Ruth Merkatz, Special Assistant to the Commissioner of Food and Drugs for Women's Health. With me today is Grant Bagley, who is a Medical Officer in the Office of Health Affairs. We appreciate the opportunity to be here to discuss with you the initiatives of the Food and Drug Administration (FDA) to improve the status of women's health in this country.

As a public health agency, FDA traditionally has made a substantial commitment to improving the status of women's health. We encourage the development and availability of products beneficial to women's health. The Agency also has a number of activities aimed at developing and promoting information to assist women, their health care providers, and industry.

Since 1983, the Agency also has been a major participant in the overall efforts of the Public Health Service (PHS) to examine and assess the status of women's health in the U.S. For the past 10 years, FDA has worked closely with the PHS Coordinating Committee on Women's Health Issues to raise national awareness about women's health concerns. In addition to making decisions about the regulation of products for women, we have established a program that focuses on coalition-building, networking, greater participation by women in FDA activities and providing information directed exclusively to women.

Dr. Kessler has reaffirmed this long-standing commitment and his own personal interest in women's health by establishing my position to serve as a focal point within the Agency for these important initiatives.

Before discussing specifically some of the key initiatives underway at FDA in the area of women's health and the issues you raised in your letter of invitation, I believe it might be helpful to describe briefly the new drug development review and approval process, and how the process facilitates the goal we all hope to achieve--healthier and better informed women.

NEW DRUG APPROVAL PROCESS

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

In order to study the safety and effectiveness of an unapproved new drug, the sponsor is required first to file an Investigational New Drug (IND) application with FDA. Once accepted, the IND allows the sponsor to ship the drug in interstate commerce for research purposes only. The responsibility for the clinical trials and distribution of the drug falls upon the sponsor of the IND.

When the sponsor determines that adequate and well-controlled studies showing the drug is safe and effective have been carried out, that information is submitted to FDA in the form of an NDA. The NDA also must contain information from preclinical studies in animals regarding the pharmacology and toxicology of the drug. Information is also required on the manufacturing procedures and controls used in producing the drug. After comprehensive review by FDA, and response by the sponsor to FDA's requests for any needed additional data or analyses, the NDA is either approved or not approved. As part of this review, the new drug is often considered by an advisory committee comprised of acknowledged experts in their fields. Upon approval, the drug may be marketed.

I should mention here that efforts in recent years to streamline the drug approval process have emphasized early interaction between FDA and sponsors of applications in an effort to facilitate the development and availability of new

drugs. An example of the importance of good Agency-industry interaction occurred during the review of Norplant, the recently approved contraceptive implant. Resolution of a number of problems were expedited through enhanced communications and resulted in the timely review and approval of this important new contraceptive option.

For your information, since you expressed an interest in the status of the development of RU-486, the Agency now holds a number of active INDs for this drug for the study of various diseases, including meningiomas, Cushing's syndrome, Alzheimer's diseases and endometriosis. Information relative to these studies has already been made public. It is important to emphasize that there are restrictions on FDA relative to the release of information on file with the Agency. Certaim information related to applications that are under review at FDA is considered confidential and is not releasable to the public, or in public hearings, under the Agency's Freedom of Information Act regulations.

WOMEN IN CLINICAL TRIALS

I would also like to comment briefly on FDA activity with respect to the inclusion of women as participants in drug development.

We have heard concern expressed that women are sometimes under-represented in clinical trials of therapies that women will use. This is a valid concern, and we share it. It does not appear, however, that women are systematically under-represented in the data submitted by drug manufacturers to support approval of new drug applications.

This was shown in surveys of NDA's carried out in 1983 and again in 1988. The surveys were performed primarily to assess the participation of the elderly in clinical trials, but we also collected data on the proportion of women in trials. The survey results indicated that, in general, women are represented in clinical trials to about the extent that the prevalence in women of the disease being treated by the test drug would suggest. Thus, women were more than half of the patients in studies for arthritis (anti-inflammatory drugs, e.g., ketoprofen and diclofenac), a condition somewhat more prevalent in women. Women comprised about half the patients given sleeping pills (triazolam) or most antibiotics (cefoperazone, netilmycin, but 1/3 of the patients given cefotiam), and comprised a smaller proportion (about 1/3) of patients studied for drugs to treat such cardiovascular diseases as heart failure and angina pectoris (nicardipine, carteolol, verapamil, bumetanide), which are more common in men for most ages groups. A more recent survey by the General

Accounting Office is expected to be released this summer, and we will evaluate that report as part of our policy discussions.

In general, the population expected to use a product should determine who is to be studied. Population-specific questions about safety, efficacy, dose and administration schedules should be addressed so that the drug's labeling may be adequate to convey complete and accurate information to prescribing physicians. Although this principle is applied in current guidelines, the Agency will revise its guideline, General Considerations for the Clinical Evaluation of Drugs, to state explicitly that clinical studies of a drug should include a reasonable sample of the patients who will eventually use the drug. The importance of gender-specific analyses has already been emphasized by the Agency. In 1988, our Guideline for the Format and Content of the Clinical and Statistical Data Section of an Application emphasized the need to look for the possible relationship of favorable or unfavorable responses to drugs to demographic features such as age, gender or race.

FDA does impose one restriction on the inclusion of women in clinical studies. For routine drugs, women of child-bearing potential are excluded from very early clinical trials, including the earliest, so called phase 1 safety (tolerance) studies, and the first controlled trials. This exclusion, intended to protect a fetus from possible exposure to a

teratogenic substance when there is little potential benefit, does not apply to studies of drugs being investigated for life-threatening diseases, such as cancer and AIDS. These studies are routinely open to young women.

This restriction presents an important sociopolitical issue, and the policy is being reconsidered. It is very likely that it would at least be modified to allow women of child-bearing potential to participate in early trials of drugs for conditions for which no good alternative therapy exists, and we are planning a meeting to discuss the social, legal, and ethical issues related to studies in general in women.

We maintain a close working relationship with the Office of Research on Women's Health at the National Institutes of Health, and also with the PHS Women's Health Office, which coordinates these issues across the agencies within the PHS. Together, we have developed a scientific agenda for a June conference on the pharmacokinetics of drugs in women, to be held in conjunction with the Institute of Medicine. This forum will lay the groundwork for determining what we know and what we need to know about the pharmacokinetics of drugs in women.

OTHER INITIATIVES

Let me describe several other initiatives that are underway at the Agency.

Breast and Cervical Cancer. FDA, the Centers for Disease Control and the National Cancer Institute have developed the "National Strategic Plan for the Early Detection and Control of Breast and Cervical Cancer." This coordinated effort addresses: public education, professional education and medical practice, quality assurance, breast and cervical screening, surveillance and epidemiology.

Mammography. As you know, mammography machines are regulated by FDA as medical devices. In November 1990, FDA published the results of a survey which demonstrated that the quality of mammograms had significantly improved over the past five years. This improved imagery was achieved with only a slight increase in radiation to the patient. The radiation levels remained within accepted limits. FDA continues to conduct research on methods to improve mammography equipment and screening systems, and plans to survey mammography equipment again this year. I should note also that FDA recommends, when possible, that women use mammography facilities accredited by the American College of Radiology, and certified under the Clinical Laboratories Improvement Act by the Medicare program.

Breast Implants. Following the recommendation of its expert advisory committee, FDA restricted significantly the use of silicone gel-filled breast implants. Through a number of studies, information on the safety of these devices will be evaluated. FDA also co-chairs, with NIH, a PHS task force to develop a research strategy to study issues related to breast implants. Specifically, this group will review any ongoing clinical studies, determine the design of additional studies and consider epidemiologic approaches to evaluating the incidence of disease in implant recipients, including immune diseases and cancer.

In the meantime, FDA continues to operate a toll free information service to advise and assist women on this issue. The toll free number operates Monday through Friday, from 9 a.m. to 7 p.m., and is staffed with trained information specialists. Consumers can get answers to their questions about breast implants by calling 1-800-532-4440 or TDD 1-800-688-6167, for the hearing impaired. As of April 30, FDA has responded to over 34,000 telephone calls and has sent written information to over 26,000 consumers.

Female Barrier Devices. In recognition of the alarming increase in sexually transmitted diseases, especially AIDS, FDA has developed a guidance document to assist manufacturers and researchers in the design of preclinical and clinical studies

that would ultimately lead to marketing approval of female barrier devices.

AIDS. FDA is involved in a number of AIDS-related activities. These include the PHS AIDS Clinical Trials Information Service which provides information on drug trials underway and interaction with community groups affected by the AIDS epidemic. Special emphasis has been placed on issues related to people of color and to women and children.

FDA is also a member of the PHS Panel on Women, Adolescents, and Children with HIV Infection and AIDS, co-chaired by the Surgeon General, Dr. Antonia Novello. The Panel has been instrumental in conducting conferences aimed at issues related to women and the pediatric AIDS community.

Women and Medications. FDA, in conjunction with the National Council on Patient Information and Education, has developed a campaign concerning the use and dispensing of medicines by women. The campaign will promote safer and more effective use of medicines through improved communication between women, who are the primary users and dispensers of medicines within the family, and health care providers. The major materials for this campaign have included a research-based article on women and medications (45,000 copies were distributed through various networks); a brochure (nearly 70,000 copies have been

distributed to date); and public service print and radio advertisements.

Recruitment. Women hold key policy-making positions within FDA. Increasing numbers of women, whose official responsibilities include issues related to women's health initiatives at FDA, are now in top decision-making positions within the Agency. These include the Deputy Commissioner for Operations, the Deputy Commissioner for External Affairs, the Senior Advisor to the Commissioner, the Chief Counsel, the Senior Advisor to the Commissioner for Management and Information, the Chief Mediator/Ombudsman, and the Directors of the Center for Biologics Evaluation and Research and the Office of Orphan Product Development. These women from diverse backgrounds--physicians, basic scientists, administrators, and lawyers-- are able to provide a balanced view of the issues so important to women's health.

CONCLUSION

I would like to conclude by discussing the PHS Action Plan for Women's Health, and FDA's initiatives in furthering the goals identified by PHS. Through this plan, the PHS has reaffirmed women's health as a national public health priority. A copy of the Action Plan is submitted for the record.

FDA has long been an advocate for focusing on and responding to the issues relevant to women's health. To meet the goals established by the action plan, FDA will develop further networks and health education programs that support women in their efforts to learn about sound health practices and the safe use of drugs and devices. We also expect to revise our guidelines relative to clinical testing of drugs to emphasize the importance of including in the studies the full spectrum of patients who will eventually use the drug. We believe that the sustained efforts underway will improve the health and quality of life for the Nation's women.

This concludes my prepared testimony. I will be happy to respond to any question you may have.

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, December 8, 1992

The Honorable Ron Wyden
Chairman, Subcommittee on
Regulation and Business Opportunities
Room B363, Rayburn Housse Office Building
Washington, DC 20515
USA

Dear Congressman Wyden,

Thank you for your letter concerning clinical testing and commercial distribution of RU 486 in the United States. In your capacity as Chairman of the Committee on Small Business of the US House of Representatives, we appreciate your courtesy in bringing to our attention the expressions of interest of small companies in working with us.

With regard to your comments on the New York Times article, please do not take a declaration made to a journalist by one of Roussel Uclaf's collaborators as an official statement by the Board of Directors.

We are perfectly aware that the change in the opinion of the American administration will, no doubt, take place as soon as President-elect Bill Clinton has been sworn in.

I can assure you that Roussel Uclaf is not "stalling", as press reports of your news conference stated. Quite to the contrary, we have begun to review our policy regarding the Mifepristone product. As you well know, this is an extremely complex issue with many ramifications that must be, and will be examined carefully, objectively and thoroughly.

Indeed, there are many possibilities to carry out clinical trials in your country: through the Population Council, Family Planning organizations, by licensing-out to third parties...

.../...

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

For your information, a meeting with FDA representatives has been scheduled at their request, and will take place in Paris on December 14, 1992.

We are hoping to be able to have a clearer picture of the situation before the end of January 1993.

With reference to the case of Mr. Grow, I would like to draw your attention to the fact that studies are presently underway in the United States for applications other than voluntary pregnancy termination, and you will find below a summary on the RU 486 clinical trials.

- Ovulation blockade in women with mechanical contraception (Pr. L. Niemann, National Institutes of Health):

It is important to note that compassionate use of the drug creates many problems:

- since it is an empirical attitude, there is no possible conclusion regarding efficacy and tolerance: the information for a given patient is useless for further patients;
- lack of facilities for Roussel Uclaf to handle the drug in the United States;
- the adverse effects are almost impossible to document properly.

The compassionate use of the compound must be restricted to those cases for which there is no real alternative.

Sincerely,

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 20515-6315

TO: _____

FROM: STEVE JENNING

ABOUT:

SEE FDA
REFERENCE ON P. 2
OF LETTER.
WHAT GIVES?

3 PAGES (INCLUDING COVER)

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

AF
9209093

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, December 17, 1992

DEC 17 11 55 AM '92

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

Dear Doctor Kessler,

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

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

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

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

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

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

Yours sincerely,

92-8252

35, Boulevard des Invalides - "Gué" Paris

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 22, 1993

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

Dear Dr. Sakiz:

This letter is pursuant to my letter to you of December 15, 1992, and confirms my meeting with you and Dr. Andre Ulmann to take place as soon as possible. I understand that sometime during the first 3 days of February may be possible.

The purpose of the meeting is to discuss possible therapeutic uses of anti-progestational drugs and, in particular, our interest in receiving a New Drug Application for approval of mifepristone for interruption of early pregnancy. Several of my colleagues will also attend the meeting.

I am pleased that you and Dr. Ulmann are able to respond to my invitation to discuss these important issues. My office will work with yours in establishing when we shall meet.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 22, 1993

Andre Ulmann, M.D., Ph.D.
Louise Silvestre, M.D.
Roussel Sante R. et D.
Domaine Therapeutique Endocrinologie
Roussel Uclaf
Romainville, France

Dear Drs. Ulmann and Silvestre:

The Food and Drug Administration has received a request for assistance in obtaining a "compassionate IND" for the use of mifepristone (RU-486) in the treatment of [redacted] a patient with recurrent meningioma. I have spoken to her physician, [redacted] and have informed him that we would be willing to approve a single patient IND for [redacted] if you agree to provide the drug. Although [redacted] may be eligible for the [redacted] she is unwilling to be randomized to placebo and is unable to travel to one of the study centers. In her letter she hints that she may commit suicide if her disease continues to progress. Because of her psychological state, we ask that you give her request serious consideration. In addition, if she does not receive the drug she plans to make her case to the media. The media coverage is likely to generate even more requests for the drug. Someone from the Commissioner's office is scheduled to be interviewed about the request on CNN on Tuesday, January 26, 1993.

We understand that you are concerned about the number of requests that you have received for the drug for single patient INDs for unresectable meningioma. We share your concern and agree that whenever possible patients should be encouraged to participate in the ongoing Phase III study. However, for a variety of reasons, some patients are unwilling or unable to participate in a study. As long as accrual to the Phase III study is not significantly compromised, it is our policy to consider individual patient IND's in situations where there is sufficient reason to expect benefit and there is no satisfactory alternative therapy. It would be preferable to enter these patients on a single open Phase II study so that data could be collected on response and toxicity.

We would be happy to discuss your concerns with you and how best to handle this situation. My telephone number is

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ON ORIGINAL

[redacted] and fax numbers are [redacted] or [redacted]

We look forward to your response.

Sincerely,

Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

With: Andre Ulmann, M.D., Ph.D.
Firm: Roussel Uclaf
Date: January 25, 1993
Drug: mifepristone (RU-486)
Telephone#: 011-33-1-49-91-48-21

Dr. Ulmann called regarding my letter of January 22, 1993. He asked what we should do regarding [redacted] request for a compassionate IND for the use of mifepristone in the treatment of her meningioma. I told him that I was in general agreement with their policy of encouraging all eligible patients to enroll in the — phase III study. However, since [redacted] is unwilling and is hinting at suicide, I recommended that we approve the request. He agreed to supply the drug for [redacted] and also for another patient, [redacted].

We then discussed how the many compassionate requests should be handled. We agreed that patients should be strongly encouraged to enroll in the — study. However, patients who were not eligible for the study or who could not participate for a very good reason would be considered for individual INDs. Dr. Ulmann emphasized that physicians would have to document the reasons that an eligible patient could not participate. Belief that the drug is effective and unwillingness to be randomized to placebo would not be sufficient since patients randomized to placebo could cross over to mifepristone at progression.

Dr. Ulmann also expressed concern about the quality of the data received on the compassionate IND patients. He was especially concerned about adverse reaction data. We discussed the possibility of an open phase II study. He stated that they send a protocol with information on the drug and case report forms to investigators but don't always receive completed forms. I told him that we would ask investigators to send us copies of the forms and could help if any investigators were delinquent. We agreed to call if there were any probler-

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APPEARS THIS WAY ON ORIGINAL

THE WHITE HOUSE

WASHINGTON

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF HEALTH AND HUMAN SERVICES

SUBJECT: Importation of RU-486

In Import Alert 66-47, the Food and Drug Administration ("FDA") excluded the drug Mifepristone -- commonly known as RU-486 -- from the list of drugs that individuals can import into the United States for their "personal use," although the drugs have not yet been approved for distribution by the FDA. (See FDA Regulatory Procedures Manual, Chapter 9-71.) Import Alert 66-47 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

9300432

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release January 22, 1993

REMARKS BY THE PRESIDENT
DURING SIGNING OF PRESIDENTIAL MEMORANDA

The Roosevelt Room

3:22 P.M. EST

THE PRESIDENT: Please sit down, ladies and gentlemen.

Today I am acting to separate our national health and medical policy from the divisive conflict over abortion. This conflict, which stems from the Roe v. Wade decision of 20 years ago has brought to a halt promising research on treatment for serious conditions and diseases that affect millions of Americans -- millions of American men, women and children who include the members of my family and friends of mine and I'm sure virtually every other set of family and friends in the United States.

We must free science and medicine from the grasp of politics and give all Americans access to the very latest and best medical treatments.

Today I am directing Secretary of Health and Human Services Shalala immediately to lift the moratorium on federal funding for research involving transplantation of fetal tissue. This moratorium, which was first imposed in 1988, was extended indefinitely in 1988 despite the recommendation of a blue ribbon National Institute of Health advisory panel that it be ended. Five years later, the evidence is overwhelming. The moratorium has dramatically limited the development of possible treatment for millions of individuals who suffer from serious disorders, including Parkinson's disease, Alzheimer's disease, diabetes and leukemia. We must let medicine and science proceed unencumbered by anti-abortion politics.

Today also marks the beginning of a new national reproductive health policy that aims to prevent unintended pregnancies. Our administration is committed to providing the kind of prenatal care, child care and family and medical leave that will lead to healthy childbearing and support America's families.

As a nation, our goal should be to protect individual freedom while fostering responsible decision-making, an approach that seeks to protect the right to choose while reducing the number of abortions. Our vision should be of an America where abortion is safe and legal, but rare.

Let me also say that our administration is particularly concerned with the epidemic of teenage pregnancy. The greatest human cost of our continuing national debate over reproductive policy is borne by our children and by their children. A few teenagers choose to have and raise children, and we must help them to succeed. But for millions a teen pregnancy is unintended, leaving the young woman and her partner totally unprepared for the responsibilities of parenthood. The social and economic price paid today and for the last several years by our nation is enormous.

So today I am also directing Secretary Shalala to act immediately to implement her intended suspension of the Title X family planning regulations that are also known as the "gag rule."

MORE

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: The Title X "Gag Rule"

Title X of the Public Health Services Act provides Federal funding for family planning clinics to provide services for low-income patients. The Act specifies that Title X funds may not be used for the performance of abortions, but places no restrictions on the ability of clinics that receive Title X funds to provide abortion counseling and referrals or to perform abortions using non-Title X funds. During the first 18 years of the program, medical professionals at Title X clinics provided complete, uncensored information, including nondirective abortion counseling. In February 1988, the Department of Health and Human Services adopted regulations, which have become known as the "Gag Rule," prohibiting Title X recipients from providing their patients with information, counseling, or referrals concerning abortion. Subsequent attempts by the Bush Administration to modify the Gag Rule and ensuing litigation have created confusion and uncertainty about the current legal status of the regulations.

The Gag Rule endangers women's lives and health by preventing them from receiving complete and accurate medical information and interferes with the doctor-patient relationship by prohibiting information that medical professionals are otherwise ethically and legally required to provide to their patients. Furthermore, the Gag Rule contravenes the clear intent of a majority of the members of both the United States Senate and House of Representatives, which twice passed legislation to block the Gag Rule's enforcement but failed to override Presidential vetoes.

For these reasons, you have informed me that you will suspend the Gag Rule pending the promulgation of new regulations in accordance with the "notice and comment" procedures of the Administrative Procedure Act. I hereby direct you to take that action as soon as possible. I further direct that, within 30 days, you publish in the Federal Register new proposed regulations for public comment.

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

WILLIAM J. CLINTON

# # #

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: Federal Funding of Fetal Tissue Transplantation Research

On March 22, 1988, the Assistant Secretary for Health of Health and Human Services ("HHS") imposed a temporary moratorium on Federal funding of research involving transplantation of fetal tissue from induced abortions. Contrary to the recommendations of a National Institutes of Health advisory panel, on November 2, 1989, the Secretary of Health and Human Services extended the moratorium indefinitely. This moratorium has significantly hampered the development of possible treatments for individuals afflicted with serious diseases and disorders, such as Parkinson's disease, Alzheimer's disease, diabetes, and leukemia. Accordingly, I hereby direct that you immediately lift the moratorium.

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

WILLIAM J. CLINTON

# # #

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

# # #

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release January 22, 1993

January 22, 1993

MEMORANDUM FOR THE SECRETARY OF DEFENSE

SUBJECT: Privately Funded Abortions at Military Hospitals

Section 1093 of title 10 of the United States Code prohibits the use of Department of Defense ("DOD") funds to perform abortions except where the life of a woman would be endangered if the fetus were carried to term. By memoranda of December 21, 1987, and June 21, 1988, DOD has gone beyond what I am informed are the requirements of the statute and has banned all abortions at U.S. military facilities, even where the procedure is privately funded. This ban is unwarranted. Accordingly, I hereby direct that you reverse the ban immediately and permit abortion services to be provided, if paid for entirely with non-DOD funds and in accordance with other relevant DOD policies and procedures.

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

WILLIAM J. CLINTON

# # #

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release January 22, 1993

January 22, 1993

MEMORANDUM FOR THE ACTING ADMINISTRATOR OF THE AGENCY FOR INTERNATIONAL DEVELOPMENT

SUBJECT: AID Family Planning Grants/Mexico City Policy

The Foreign Assistance Act of 1961 prohibits nongovernmental organizations ("NGO's") that receive Federal funds from using those funds "to pay for the performance of abortions as a method of family planning, or to motivate or coerce any person to practice abortions." (22 U.S.C. 2151b(f)(1)). The August 1984 announcement by President Reagan of what has become known as the "Mexico City Policy" directed the Agency for International Development ("AID") to expand this limitation and withhold AID funds from NGO's that engage in a wide range of activities, including providing advice, counseling, or information regarding abortion, or lobbying a foreign government to legalize or make abortion available. These conditions have been imposed even where an NGO uses non-AID funds for abortion-related activities.

These excessively broad anti-abortion conditions are unwarranted. I am informed that the conditions are not mandated by the Foreign Assistance Act or any other law. Moreover, they have undermined efforts to promote safe and efficacious family planning programs in foreign nations. Accordingly, I hereby direct that AID remove the conditions not explicitly mandated by the Foreign Assistance Act or any other law from all current AID grants to NGO's and exclude them from future grants.

WILLIAM J. CLINTON

# # #

MAIL ALL-STATES CANADA 32:PHF00500 EX 'TALK PAPER/T93-10 DTD 02-25-93'

TO: NR-1 (STATE HEALTH OFFICERS)
NR-3 (BOARDS OF PHARMACY)
NR-4 THRU NR-16, NR-39 THRU NR-43 (STATE DRUG OFFICIALS)

INFO: ASTHO - DAVID FISCHER
NABP - CARMEN CATIZONE
AFDO - WHITNEY ALMQUIST
NAAG - CLAY FRIEDMAN
NASDA - RICHARD KIRCHHOFF
MEXICO - DRA. MERCEDES JUAN

FROM: _____ DIVISION OF FEDERAL-STATE RELATIONS, ORO/FDA

DATE: FEBRUARY 25, 1993

SUBJECT: TALK PAPER ON RU-486

FDA is receiving inquiries about a Feb. 24, 1993, meeting at FDA headquarters with the French company Roussel-Uclaf, the manufacturer of RU-486, a drug approved as an abortifacient in France, England and Sweden, but not in the United States. The agency has said that it would welcome a New Drug Application (NDA) for RU-486 to allow it to determine if the drug represents a safe and effective alternative to surgery.

The Feb. 24 discussions concerned clinical and manufacturing data on the drug, focusing on the types of data FDA would need in considering an NDA for RU-486. The manufacturer pointed out that an early step toward approval would be a large clinical trial in which U.S. physicians would be trained in the use of RU-486, and would administer the drug to women participating in the trial. Data could also be collected on how the drug could be safely and effectively administered in typical medical settings in this country.

While asserting that RU-486 should be made available in the United States, the firm emphasized the importance of finding a way to achieve that goal without the involvement of Roussel-Uclaf. Among the possible avenues discussed were a U.S. pharmaceutical firm, a research center or a university.

FDA and Roussel-Uclaf agreed to continue to work on this matter until remaining issues can be resolved. The company also said it remains strongly committed to continuing to make the drug available for research on other

potential uses.

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ON ORIGINAL

From: FDA901 Delivered: Thu 25-Feb-93 12:48 EST Sys 157
Subject: TALK PAPER
Mail Id: IPM-157-930225-115311233

TO: All Field Offices, District Offices and Resident Posts, attn: RFDDs, DDs, Public Affairs Specialists, Small Business Representatives, and Recall Coordinators
ORA Federal State Relations
ORA Emergency Operations
ORA Compliance Guidelines Branch
ORA Office of Enforcement
ORA, Office of Regional Operations
Director, NCTR
[redacted], ORA Consumer Affairs
Office of Training and Assistance, CDRH
[redacted], Device Evaluation, CDRH
CBER Congressional Public Affairs
CDER Compliance
CDER Consumer and Professional Affairs
CFSAN, Dauphin Island, Ala.
CFSAN, Davisville, Rhode Island
CFSAN, Consumer Affairs Representative
All PASs

FR: FDA Press Office

NOTE TO CDB COMPLIANCE: Please hand-deliver a copy of this to [redacted] in Consumer and Professional Relations, Rm. 221 Metro Park North.

TALK PAPER

T93-10
Feb. 25, 1993

Lawrence Bachorik
(301) 443-1130

MEETING WITH ROUSSEL-UCLAF ON RU-486

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FDA and Roussel-Uclaf agreed to continue to work on this matter until remaining issues can be resolved. The company also said it remains strongly committed to continuing to make the drug available for research on other potential uses.

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FDA

TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T93-10
Feb. 25, 1993

Lawrence Bachorik
(301) 443-1130

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21

March 4, 1993

Via Fax

Mr. Edouard Sakiz
President
Laboratories Roussel-Uclaf SA
35 bvd. des Invalides
BP 12007, 75323 Paris
Cedex 07
France

Dear Mr. Sakis:

During the past two years I have been in touch with several members of your company, our FDA, and responsible members of the medical community indicating the willingness of _____ to develop and commercialize RU 486 in North America.

Please accept this letter as a firm indication of our interest in RU 486 and willingness to enter into exclusive licensing discussions for rights to this drug in our home markets.

For your background and information I enclose materials describing our firm. I am at your disposal regarding a meeting to commence discussions with Roussel-Uclaf.

Very sincerely yours,

_____

_____

President

cc: Mrs. Donna Shalala
Senator W. Bradley
Senator F. Lautenberg

FYI
CCC has no record of stated

ROUSSEL UCLAF

Docteur Edouard Sakiz
Président du Directoire

Paris, March 18, 1993

Mrs. 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 Mrs. Shalala,

It was very thoughtful of you to send me a copy of your March 12 letter to Professor Wolfgang Hilger, for which I thank you very much.

The Roussel Uclaf Group and I appreciate your commitment to the expansion of safe and effective healthcare choices for American women for the termination of unwanted pregnancy. The comments contained in your letter also reflect President Clinton's determination to keep the promises he made throughout his campaign.

The message delivered to Professor Hilger will greatly contribute to progress further in order to sort out the complexities of the issues involved in any decision to make the drug available in the United States.

The meeting held last month with Dr. Kessler is already proving very rewarding as new steps are going to be considered with the help of Margaret Catley-Carlson, the President of the Population Council, who has also assured us of her support wi regard to getting clinical trials started in the United States.

In view of the clinical studies and the training program which are to be undertaken because French and US regulations concerning early termination of pregnancy are not the same, it will still take some time before RU 486 is made available to American women.

I will be pleased to keep you informed of any further development.

Yours sincerely,

9301600

35, Boulevard des Invalides 75007 Paris
Tél. + 33 (1) 40 62 44 28 Fax. + 33 (1)

PROF. DR. WOLFGANG HILGER
VORSITZENDER DES VORSTANDES
HOECHST AKTIENGESELLSCHAFT

6230 FRANKFURT AM MAIN 80
POSTFACH 8000 80
TELEFON 0 69/ 3 05-74 80

March 23, 1993

The Secretary of Health and Human Services
Mrs. Donna E. Shalala
Washington, D.C. 30201

U.S.A.

Dear Mrs. Shalala:

Many thanks for your letter of March 12, 1993, which I have received by fax.

I would like to describe the present situation in the USA as follows:

On the request of the Food and Drugs Administration, a meeting with Dr. Edouard Sakiz, President of Roussel Uclaf has taken place to discuss relevant question on the drug RU 486.

In their wide-ranging discussions both sides recognized the complexities of the issue, involved in any decision to make the drug available in the United States.

The FDA has clearly pointed out that you are very much willing to see RU 486 made available in the USA. However, the FDA accepts that Roussel Uclaf has no intention to approach the FDA to obtain marketing licence for the drug. The FDA has undertaken to approach third parties who are competant and might be interested to sponsor clinical studies and to market the drug in the USA. Because the drug is currently available only under very restricted distribution (France, the United Kingdom and Sweden) it will become necessary that the FDA will issue new regulation to control the use and distribution.

Both sides will continue their consultations to clarify the many open questions on the issue. At a later stage a common decision on how to proceed in the USA will be taken.

Yours sincerely,

Wolfgang Hilger.

93-1820

T55370 PHS

PROF. DR. WOLFGANG HILGER
[illegible]
[illegible]

[illegible]
[illegible]
[illegible]

Dr. David Kessler
Commissioner of the
Food and Drug Administration
5600 Fishers Lane, HF-40
Rockville, Maryland 20857
U.S.A.

April 15, 1993

Fax: 001-301-443-1863

Dear Dr. Kessler,

Thank you for your letter of April 14 concerning the meeting you propose on the Roussel Uclaf compound RU 486.

We are both aware that the development of RU 486 in the field of abortion has confronted us with an extremely complex social issue which is almost impossible to resolve in a way that would be acceptable to all concerned.

In spite of our position to not be involved in the marketing or production of RU 486 for the American market, we are making a considerable effort to respect your intention to make the compound available to the medical profession in the United States.

I am aware that substantial progress has been made since your last meeting with Dr. Sakiz on February 24 in Washington D.C.

If the FDA considers a clinical trial to be necessary, you know that it can be carried out by the Population Council, with whom Roussel Uclaf has a long-standing agreement on this compound.

Concerning the eventual distribution in the United States, this can only be done through third parties, as we have always indicated and as I have reiterated in my press conference on March 23.

The question of production can be resolved as indicated in the Roussel Uclaf agreement with the Population Council, which permits a transfer of their production technology to a third party.

I know that Dr. Sakiz will be meeting with you on April 20 to determine the next steps to be taken to make RU 486 available in the United States. He is the most knowledgable individual on this issue within the Hoechst organization and is fully aware of all the problems concerning RU 486. We are entirely confident that he is the best representative we could send for the meeting you have proposed. I believe that sending another representative of Hoechst would serve no useful purpose.

Be assured that I am following this matter very closely and am confident that a satisfactory solution for all parties can be found.

Sincerely yours,

W. Hilger.

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 "Seine" Paris
Tél. : 33 (1) 40 62 44 28 Fax. : 33 (1) [illegible]

HHS FACT SHEET

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mifepristone (RU-486): Brief Overview

May 16, 1994

Contact: FDA Press Office
(301) 443-1130

On Jan. 22, _ 93, in one of his first official acts, President Clinton issued a memorandum directing HHS Secretary Donna E. Shalala to assess initiatives to promote the testing and licensing of mifepristone (RU-486) in the United States.

During early 1993, Secretary Shalala and FDA Commissioner David Kessler communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace.

In April 1993, representatives of FDA, Roussel Uclaf and the Population Council, a not-for-profit organization, met to discuss U.S. clinical trials and licensing of RU-486. Over the last year, the parties continued their negotiations, culminating in the donation announced today. Roussel Uclaf will transfer, without remuneration, its United States patent rights to mifepristone to the Population Council. In turn, the Population Council will take the necessary steps to bring RU-486 to the American market.

Mifepristone was developed by the French firm Roussel Uclaf. The drug has been marketed for use to non-surgically terminate pregnancy in France, the United Kingdom and Sweden. There are several investigative trials underway with FDA for other uses of the drug, including contraception, labor induction, Cushing's syndrome, endometriosis, meningioma and breast cancer.

It must be recognized that termination of a pregnancy is not a simple medical procedure, whether it is done surgically or through a medical regimen. In France, the United Kingdom and Sweden, where RU-486 has been administered to approximately 150,000 women, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for woman who may experience excessive bleeding or other complications. Any use of mifepristone in the United States would have to follow the same type of strict distribution and use conditions.

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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Monday, May 16, 1994

Contact: Victor Sonana
(202) 690-6343

ROUSSEL UCLAF DONATES U.S. PATENT RIGHTS FOR RU-486 TO POPULATION COUNCIL

HHS Secretary Donna E. Shalala announced today that French pharmaceutical company Roussel Uclaf, at the encouragement of the Clinton administration, is donating, without remuneration, its United States patent rights for mifepristone (RU-486) to the Population Council, Inc., a not-for-profit corporation.

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

"We strongly believe that women in America should have access to the full range of safe and effective alternatives to surgical abortion," Shalala said. "The donation announced today is a big step in that direction."

On Jan. 22, 1993, President Clinton signed a Presidential Memorandum directing the Department of Health and Human Services to assess initiatives to promote the testing and licensing of RU-486 in the United States.

- More -

Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.

Shalala emphasized, however, that the donation does not mean RU-486 has been approved for use in the United States. The Population Council must conduct clinical trials, identify a manufacturer and submit a new drug application to the Food and Drug Administration.

"The FDA will do all it can to quickly evaluate mifepristone," said Shalala. "FDA's decision will be based solely on the scientific and medical evidence as to the safety and efficacy of the drug. That is our responsibility to the women of America."

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APPEARS THIS WAY
ON ORIGINAL

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Monday, May 16, 1994

Contact: Victor Zonana
(202) 690-6343

ROUSSEL UCLAF DONATES U.S. PATENT RIGHTS FOR RU-486 TO POPULATION COUNCIL

HHS Secretary Donna E. Shalala announced today that French pharmaceutical company Roussel Uclaf, at the encouragement of the Clinton administration, is donating, without remuneration, its United States patent rights for mifepristone (RU-486) to the Population Council, Inc., a not-for-profit corporation.

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

"We strongly believe that women in America should have access to the full range of safe and effective alternatives to surgical abortion," Shalala said. "The donation announced today is a big step in that direction."

On Jan. 22, 1993, President Clinton signed a Presidential Memorandum directing the Department of Health and Human Services to assess initiatives to promote the testing and licensing of RU-486 in the United States.

- More -

HHS FACT SHEET

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mifepristone (RU-486): Brief Overview

May 16, 1994

Contact: FDA Press Office
(301) 443-1130

On Jan. 22, 1993, in one of his first official acts, President Clinton issued a memorandum directing HHS Secretary Donna E. Shalala to assess initiatives to promote the testing and licensing of mifepristone (RU-486) in the United States.

During early 1993, Secretary Shalala and FDA Commissioner David Kessler communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace.

In April 1993, representatives of FDA, Roussel Uclaf and the Population Council, a not-for-profit organization, met to discuss U.S. clinical trials and licensing of RU-486. Over the last year, the parties continued their negotiations, culminating in the donation announced today. Roussel Uclaf will transfer, without remuneration, its United States patent rights to mifepristone to the Population Council. In turn, the Population Council will take the necessary steps to bring RU-486 to the American market.

Mifepristone was developed by the French firm Roussel Uclaf. The drug has been marketed for use to non-surgically terminate pregnancy in France, the United Kingdom and Sweden. There are several investigative trials underway with FDA for other uses of the drug, including contraception, labor induction, Cushing's syndrome, endometriosis, meningioma and breast cancer.

It must be recognized that termination of a pregnancy is not a simple medical procedure, whether it is done surgically or through a medical regimen. In France, the United Kingdom and Sweden, where RU-486 has been administered to approximately 150,000 woman, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for woman who may experience excessive bleeding or other complications. Any use of mifepristone in the United States would have to follow the same type of strict distribution and use conditions.

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AMBASSADE DE FRANCE AUX ETATS-UNIS

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Washington, DC 20007
Téléphone: (202) 944-6232
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Le Conseiller
pour les Affaires sociales

PC/rmj

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

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FDA
EXECUTIVE SECRETARIAT

AMBASSADE DE FRANCE AUX ETATS-UNIS

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Washington, DC, 20007
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Le Conseiller
pour les Affaires sociales

PC/rmj

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

JUN 16 1994

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunities and Technology
Committee on Small Business
House of Representatives
Washington, D.C. 20515-6318

Dear Mr. Chairman:

As requested in your May 25, 1994 memo, we have enclosed a copy of the transcript with corrections made in the FDA witness' testimony for the May 16, 1994 hearing on RU-486.

If we can be of any further assistance, please let us know.

Sincerely,

Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure:
As stated above

cc: HFW-10 (2)

R/D: ____ :6/13/94
F/T:dj:6/14/94 (s:\wp____\94-4927)
(Testimony Corrections - RU-486)

APPEARS THIS WAY
ON ORIGINAL

103d Congress

United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Technology
B-363 Rayburn House Office Building
Washington, DC 20515-6315

May 24, 1994

TO: Witnesses
Hearing on RU 486
May 16, 1994

FROM: Ron Wyden, Chairman
Subcommittee on Regulation, Business Opportunities
and Technology

SUBJECT: Testimony Corrections

Thank you, again, for participating as a witness at the subcommittee's recent hearing.

The subcommittee normally requests that witnesses themselves correct the rough transcript of their spoken testimony in order to complete the final, published hearing reocrd. Attached is the transcript from your recent testimony. We request that you make your corrections according to the following guidelines:

-- Changes should be to correct grammar, spelling and punctuation, only. Corrections should not change the obvious intent or meaning of the statement as it appears in the transcript.

-- You may wish to keep a copy of your corrections for your own file.

-- The subcommittee will keep the hearing record open for changes for a period of 45 days beginning from the date of the hearing. Corrections should be submitted within that time period.

-- Corrections should be returned to the subcommittee at B-363 Rayburn House Office Building, Washington, D.C. 20515.

Again, I appreciate your help in this matter. Should you have any questions regarding this request, please contact Steve Jenning or Grady Forrer of the subcommittee staff at (202) 225-7797.

94-4927

TESTIMONY OF HON. DAVID KESSLER, M.D., COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION, WASHINGTON, D.C., ACCOMPANIED BY MARY PENDERGAST, DEPUTY COMMISSIONER/ SENIOR ADVISOR TO THE COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION

Dr. KESSLER. Thank you very much, Mr. Chairman. I am joined by my colleague, Ms. Mary Pendergast, who is Deputy Commissioner/ Senior Advisor to the Commissioner at the Food and Drug Administration.

Mr. Chairman, the Food and Drug Administration has encouraged the submission of a new drug application for RU-486 for interruption of early pregnancy so that we can determine whether it is safe and effective for that indication. If there is a safe and effective medical alternative to any surgical procedure, American women should have access to that drug regimen.

We cannot form, however, any definitive conclusions about the drug's safety and effectiveness or approve it for marketing in the United States without first reviewing the studies and other data that would be submitted in a new drug application.

On January 22nd, 1993, President Clinton issued a memorandum to the Secretary of Health and Human Services directing her to assess initiatives to promote the testing and licensing in the United States of RU-486. In response,

FDA's efforts have been focused on encouraging and facilitating the submission of a new drug application.

Immediately after the President issued the memorandum, I wrote to Dr. Edward Sakiz, President of Roussel Uclaf, and requested a meeting to discuss the possible therapeutic uses of anti-progestational drugs, and in particular FDA's interest in receiving a new drug application for RU-486 for interruption of early pregnancy.

Both Secretary Shalala and I also let Heochst AG, Roussel Uclaf's parent corporation, know of our interest. On February 24th, 1993, senior representatives of FDA and Roussel Uclaf met to discuss the clinical and manufacturing data that FDA would need to review as part of a new drug application for an abortifacient indication.

At that meeting, FDA received a strong commitment from Dr. Sakiz that he would find a way to bring RU-486 to the U.S. market. Doctor Sakiz stated that Roussel Uclaf would not be directly involved, but instead would work through a third party in the United States, Dr. Sakiz also committed to making the drug available for research on other potential uses.

FDA and Roussel Uclaf agreed to continue to work on this matter until remaining issues could be resolved. At an April 20th, 1993 meeting at FDA, Roussel Uclaf indicated its willingness to modify its 1982 contract with the

Population Council, a nonprofit scientific and technical organization. These modifications would permit the Population Council and its sublicensees to produce, test, and distribute RU-486 in the United States.

The Population Council agreed to work to identify a manufacturer for RU-486 for the United States market and to begin clinical trials to test the drug in the United States. At that point, we thought the clinical trials on RU-486 would begin soon in the United States. This proved not to be the case.

Before the Population Council would begin clinical trials, the Population Council and Roussel Uclaf undertook complex negotiations pertaining to the transfer of the RU-486 patents and the way the drug would be distributed in the United States. After a year of these negotiations, on April 14th, 1994, Secretary Shalala and senior department officials, including Ms. Pendergast and myself, met with the heads of Roussel Uclaf and the Population Council.

At that meeting, the parties indicated their willingness to continue their negotiations, and the Secretary made it clear to the negotiating parties that agreement on all outstanding issues should be reached no later than May 15th, 1994.

We are pleased that Roussel Uclaf and the Population Council have concluded their negotiations, and that Roussel

Uclaf has donated the patents on RU-486 without remuneration. We anticipate that the Population Council will now pursue the clinical testing of RU-486 in the United States. We, the Food and Drug Administration, will work with the Population Council to make certain that their clinical trials are well-designed and carefully conducted, in order to provide useful information on how the drug might be properly used in this country. FDA will review the application carefully under appropriate medical and scientific criteria.

It should be recognized that the termination of a pregnancy is not a simple procedure. Whether it is done surgically or through a medical regimen. Women should not think that pregnancy termination using a medical regimen will be simple. It will not be.

In Europe where RU-486 has been used in over 150,000 women, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for women who may experience excessive bleeding and other complications. We anticipate that any use of RU-486 in the United States would have to follow strict distribution and use controls.

Ms. Pendergast, the Deputy Commissioner, and I, are prepared to answer your questions.

[The statement of Dr. Kessler follows:]

Dr. KESSLER. Mr. Chairman, we have several INDs that are in effect for the study ~~research studies for~~ of this drug. We have already looked at chemistry and pharmacology data on this drug. We have also reviewed published studies on the clinical effectiveness studies that are in the medical literature.

Obviously, an important part of our review would be to audit the studies that are published in the medical literature.

Chairman WYDEN. Now, Dr. Kessler, in the past the Agency has said that it wants to look closely at the European clinical experience with this drug. Could you briefly describe what you see as the highlights of the European experience? In effect, we would be interested in the points that are of most interest to you as a FDA regulator, as to what you saw in Europe.

Dr. KESSLER. It is probably accurate to say, Mr. Chairman, that there have been about 20 significant studies on the use of this drug, and certainly there are many other studies that have been conducted, some with smaller numbers of patients. I would estimate that there have been between 20,000 and 30,000 patients that have been enrolled in clinical trials, and as you mentioned earlier, there are over 150,000 patients that have received the drug after it has been approved in other countries.

461 Before I go to answer your question, to give you a sense of
462 what we look at, let me refer to one particular study and
463 perhaps go through that. It is a May 27th, 1993 study, that
464 was published in the New England Journal of Medicine. And
465 again, our obligation is to review data like that and to
466 audit that data.
467 The paper is senior authored by Peyron. There are two
468 series in that paper, two series and two
469 studies that are reviewed and documented. Let me just take
470 you through the first series in study one, which involved
471 488 women. The mean duration of amenorrhea was 45 days, 45
472 days from the last period. Some women had to be excluded
473 from the study. One had an ectopic pregnancy, that would
474 not be appropriate. One had longer amenorrhea, for more
475 than 49 days. There were several that were excluded for a
476 lack of appropriate follow-up.
477 The rate of effectiveness, and define that as termination
478 of pregnancy and complete expulsion, in that series of 488
479 patients, was 96.9 percent. Termination of pregnancy
480 occurred in 2.9 percent of women within 48 hours, 60 percent
481 within four hours of the second drug being administered, the
482 prostaglandin, and 33.2 percent thereafter.
483 The failures included ongoing pregnancy in 0.8 percent,
484 incomplete abortions in 1.8 percent, and surgical procedures
485 being required for heavy bleeding in 0.4 percent. All the

of settings, both public and private; is that correct?

Ms. PENDERGAST. We would anticipate that. This is a big country and women live in large cities and in small rural communities, and a major question to be asked and answered is how can you properly and safely use this drug in the wide variety of health care settings available to women?

Chairman WYDEN. And you will unquestionably in this inquiry be looking at the specific prospect of this drug being used in doctors' offices; isn't that correct?

Ms. PENDERGAST. That is correct.

Dr. KESSLER. Mr. Chairman, the issues that have concern to the Agency is to assure that appropriately trained people be the ones who are responsible for using the drug, that there be backup procedures available, and the drug be tracked so that no inappropriate use of the drug would take place. Those are the concerns. If those concerns can be met, it is likely that any setting that can meet those concerns could, in fact, carry out the procedure.

Chairman WYDEN. Doctor, I know you didn't get into all of the details of the agreement, but I am interested in asking you some questions dealing with some of the issues relating to the public interest involved in this patent gift to the Population Council.

First and foremost, we would be interested in knowing is the Government involved in any way as an indemnifier for any

party for any product liability which could occur at any point?

Dr. KESSLER. The government will not be involved in any way in indemnification of any of the parties.

Chairman WYDEN. Is it--is it fair to say that the Government acts as an interested observer of the process, but other than your job as a regulator, that is essentially the position of the Government?

Dr. KESSLER. That is correct, Mr. Chairman.

Chairman WYDEN. The Government will receive no patent rights as part of this agreement that was reached this weekend, Dr. Kessler?

Dr. KESSLER. That is correct. The Government will receive no patent rights. The gift is being made by Roussel Uclaf to the Population Council, without remuneration.

Chairman WYDEN. And the government, the Federal Government is not going to be party to any business decisions, including selection of manufacturers and distributors for the U.S. market?

Dr. KESSLER. The Government will not be part of any business decisions between the parties. We do have a responsibility and perhaps Ms. Pendergast can articulate how we view whether a manufacturer is qualified to produce a drug.

Ms. PENDERGAST. As part of any new drug application, the

company that would like to market a drug in the United States must provide to us the chemistry and manufacturing information about how the drug will be produced. And before approving any marketing application, FDA investigators go to the manufacturing site and do an inspection. So to that extent, we will be taking a look at whatever manufacturer there is, but we don't approve in advance who they might be willing to use.

Dr. KESSLER. Furthermore, Mr. Chairman, we also have responsibilities to make sure that a drug can be safely used once--if it is approved, and once it is approved. We have responsibilities with regard to the distribution and the safe use. So there is government oversight of those conditions.

Chairman WYDEN. So in terms of the regulatory process, what you are talking about, Ms. Pendergast, is essentially the kind of regulatory hurdle involving government oversight of the manufacturing processes, the good manufacturing process requirement that is essential for any manufacturer who wants to produce this drug in the United States; is that correct?

Ms. PENDERGAST. That is correct. Those are our normal processes.

Chairman WYDEN. And at this point, no one knows who that is going to be yet, because this is a decision to be made by

the Population Council?

Ms. PENDERGAST. That is correct. Perhaps the Population Council knows, but we certainly do not.

Chairman WYDEN. Let me ask you one other question with respect to the agreement and where it stands in terms of specifics. In your opinion, Dr. Kessler, is the Population Council going to get everything they need as an organization to in effect take this drug all the way through clinical trials and the approval process and in effect not have to negotiate any more agreements with the company? Is that your view, that they will get everything they need?

Dr. KESSLER. The Secretary and I and Ms. Pendergast expect that to be the case.

Chairman WYDEN. Doctor, we understand the clinical trials with this drug may start as early as this fall. Can you give us some baseline guidance as to how many locations and how many women may be involved?

Dr. KESSLER. The Population Council has an IND on file with the Food and Drug Administration. We have been told that they are planning to submit an amendment to that IND file. The information you are requesting would obviously be part of that IND file. We have been told by the Population Council that up in the range of about 2,000 women, they are expecting to design the clinical trial.

Chairman WYDEN. How long do you think the entire approval

process might take? Again, I realize that this is something that is an inexact part of the process, but in your opinion, how long do you think it might take for the approval process?

Dr. KESSLER. Let's be--let's define the word "approval". Let's talk about what needs to be done, what will be on the Population Council's clock, what will be on our clock. An application, the new drug application, needs to be submitted for the Agency to review.

We have been told by the Population Council that ~~that application,~~ they anticipate that that application will take between 9 and 16 months to prepare ~~the application~~. What needs to be done, besides collecting all the data, obviously, an important part of that application is having a manufacturing operation that is up and running. We cannot and we will not approve any application for which we are not confident that the sponsor can appropriately manufacture the drug. So a significant part of that 9 to 16 months would be getting a manufacturing process up and running. That would not be on the Food and Drug Administration's clock.

I mean our clock starts when the application is submitted. And we would anticipate, in part because we have seen a lot of preliminary data, there is still a lot we have not seen, but we would anticipate that approximately six months of actual approval time. ~~The clinical trials,~~ we have been

told by the Population Council, that they expect to have ~~these~~ clinical trials up and running by early fall.

There is an IND in effect and our review time for an IND is usually less than 30 days.

Chairman WYDEN. So really the answer to how you speed up the approval process, which is the question that I get asked, you know, continually about this, women constantly say, look, we have waited long enough, you know, it is available around the world, 150,000 women have used it. The answer to how you speed up the process even more is that the sooner the manufacturer is chosen, the sooner the process gets started. Is that correct?

Ms. PENDERGAST. That is right. I think the manufacturing process questions are the questions that will take the longest period of time.

Chairman WYDEN. One bit of housekeeping from yesteryear that I wanted to ask you about is what happens to the matter of RU-486 on the import alert list? As you know, I was very concerned about that years ago, because I always thought that imports--import alerts were issued when there was evidence of a black market or somebody was smuggling it, and when we went to try to ascertain what was behind the import alert, all we found was a bunch of letters in the file from organizations that said they thought that RU-486 was going to be the end of western civilization and it ought to be

kept out. So I am interested as to the status of RU-486 on the import alert list. And, Doctor, maybe you could tell us what that is.

Dr. KESSLER. The import alert will remain in effect. The purpose of the import alert is to make sure that no counterfeit drugs or drugs of poor quality enter the United States.

Ms. PENDERGAST. It is not possible at this time for anyone to lawfully obtain Roussel Uclaf's RU-486 to bring it into the United States. So at this time, were a woman to bring in what she thought was RU-486, the odds are it would be some sort of counterfeit or clandestinely manufactured drug of unknown safety. In addition, it is simply bad medical management for any woman to attempt to terminate a pregnancy medically by herself without very, very careful supervision of a physician.

Chairman WYDEN. I share that view, and I appreciate, Dr. Kessler, your concern about the counterfeiting. Because certainly this subcommittee over the years has received reports about those prospects and, you know, the bottom line is that the development process is moving forward, that the days of foot dragging and stalling are over and the development process is moving forward and I appreciate that.

In terms of where and when RU-486 might be used, and, again, absent the NDA from--the NDA from a sponsor, could you

project, Dr. Kessler, at what stage of pregnancy this alternative might be available?

Dr. KESSLER. The studies that we consider the most relevant discuss the indication for use in the termination of early pregnancy, that is up to 49 days of amenorrhea, 49 days from the last period. It is important to point out that 49 days from the last period is really 21 days, three weeks, from the first missed period. And therefore it is--the drug's usefulness, the drug's effectiveness, at least from the published studies, is in the early stages of pregnancy. That means for the drug to be used, the diagnosis of pregnancy needs to be made very early on.

Chairman WYDEN. With respect to the first 49 days, I gather that that still accounts for a high proportion of the current pregnancy terminations. Is that right?

Dr. KESSLER. It has been estimated that in, for example, in the French market, that as much as 20 percent, 25 percent, that it could represent that portion of the market.

Chairman WYDEN. One other question, Dr. Kessler, and then I am going to recognize my good friend from Missouri for any questions he has. Doctor, from the standpoint of a physician, could you compare RU-486 using an anti-progestin like RU-486 to a surgical abortion? I think that would be helpful to have on the record, from the standpoint of advantages, disadvantages to physicians.

Dr. KESSLER. Let me just reiterate, Mr. Chairman, that obviously we need to review the application when it is submitted. Let me tell you what is known about surgical abortions and what are the risks, what are the advantages and disadvantages of the surgical abortion.

The risk of surgical abortion includes the risk of anesthesia, the risk of infection, the risk of injury to the cervix, and risk of uterine perforation. It is a surgically invasive procedure. The advantage to a surgical abortion over a medical regimen is that in fact it could be done in probably less visits. It could be done--it can be done quicker.

The advantage of a medical procedure is that there--the advantages of the medical procedure, obviously the complications of the surgical procedures such as uterine perforation, injury to the cervix, you would not see medically. The other advantage to the medical procedure is that, in fact, surgery usually, most people who perform abortions, wait later on, don't do the procedure in the early period of pregnancy. They wait. So one of the advantages of the medical procedure is, in fact, that it could be done earlier.

There are advantages, there are disadvantages. Obviously, it awaits our full and thorough review to be able to give you a full answer.

Chairman WYDEN. But there is no requirement for anesthesia; is that correct?

Dr. KESSLER. There is no requirement for anesthesia. Certain surgical abortions are done with local anesthesia; others are done with more intense or general anesthesia.

Chairman WYDEN. Let me recognize my colleague from Missouri. We welcome him.

Mr. SKELTON. Thank you very much. As you know, Mr. Chairman, I have long had a very strong pro-life stance, but I do want to ask questions in regard to information I have that the chemical properties of this particular item is alleged to have a therapeutic value for a variety of other diseases, ranging from Cushing syndrome to meningioma, and also it deals with breast cancer. And would either one of you expand upon that for me, please?

Dr. KESSLER. There are investigational INDs that are in effect for the study of its use in other conditions. There are multiple INDs in effect. Some have been made public. As you know, we are not permitted to talk about INDs that have not been made public, but there is a range of conditions for which--

Mr. SKELTON. Well, there is a study, excuse me, it says major trials are underway to treat breast cancer. Can you speak of those, for instance?

Ms. PENDERGAST. That is correct, there are breast cancer

trials being conducted in the United States, as well as trials for meningioma, Cushing's disease and other conditions.

Mr. SKELTON. Can you name any, other than those three?

Ms. PENDERGAST. It is also being studied for diabetes, endometriosis, and for, not in this country though, for ripening the cervix, for women who have completed their pregnancy and are actually going too long. It is being studied to bring a woman to labor better than--hopefully, better than the drugs that are now being used for that purpose.

Mr. SKELTON. Are any of those studies completed?

Dr. KESSLER. There is no--I mean, again, we do not talk about, you know, those studies specifically, and whether an NDA has in fact been submitted. That is confidential information.

Mr. SKELTON. Thank you, Mr. Chairman.

Chairman WYDEN. I thank my colleague. I want to tell him that I very much appreciate him asking about the nonabortion uses, because I think we are going to see more and more of the drugs of the future in effect be these dual purpose drugs. They are going to be drugs that are going to be capable of attacking a wide variety of the cancers and the illnesses that my friend has mentioned. They are also going to be drugs that offer an alternative to surgical abortion.

And people, of course, in our country do differ as the gentleman notes on the abortion issue.

One of the efforts of this subcommittee has essentially been to say let us evaluate drugs by the book. The job of the gentleman who runs the Food and Drug Administration is to evaluate these drugs on the basis of their safety and efficacy. If they meet those standards, I am of the view that the American people want them. But I know that the gentleman has strong pro-life views and he has always been a constructive member of this subcommittee and we are going to push hard for all safe uses of this drug and appreciate the gentleman's questions.

Dr. Kessler, unless you have anything further that you would like to add, we will excuse you at this time. The subcommittee is working with you and I think on last count on something like five issues at this point, and you have always been very gracious, both with your time and with your staff's time to work with us. And I know that this puts another huge issue on a plate that is already very full and we appreciate the way you are tackling this and look forward to working with you closely in the days ahead.

Dr. KESSLER. Thank you, Mr. Chairman.

Chairman WYDEN. We will excuse you at this time. Thank you, Ms. Pendergast.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

DAVID A. KESSLER, M.D.

COMMISSIONER

OF

FOOD AND DRUGS

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON REGULATION, BUSINESS OPPORTUNITIES,

AND TECHNOLOGY

COMMITTEE ON SMALL BUSINESS

U.S. HOUSE OF REPRESENTATIVES

MAY 16, 1994

TO BE RELEASED ONLY UPON DELIVERY

Mr. Chairman, the Food and Drug Administration (FDA) has encouraged the submission of a new drug application (NDA) for mifepristone, commonly called RU-486, for interruption of early pregnancy so that we can determine whether it is safe and effective for that indication. If there is a safe and effective medical alternative to any surgical procedure, American women should have access to that drug regimen. We cannot form, however, any definitive conclusions about the drug's safety and effectiveness, or approve it for marketing in the United States, without first reviewing the studies and other data that would be submitted in a new drug application.

On January 22, 1993, President Clinton executed a memorandum to the Secretary of Health and Human Services directing her to assess initiatives to promote the testing and licensing in the United States of RU-486. In response, FDA's efforts have been focused on encouraging and facilitating the submission of an NDA.

Immediately after the President issued the memorandum, I wrote to Dr. Edouard Sakiz, President of Roussel Uclaf, and requested a meeting to discuss the possible therapeutic uses of anti-progestational drugs and, in particular, FDA's interest in receiving an NDA for RU-486 for interruption of early

pregnancy. Both the Secretary and I also let Hoechst AG, Roussel Uclaf's parent corporation, know of our interest.

On February 24, 1993, senior representatives of FDA and Roussel Uclaf met to discuss the clinical and manufacturing data on the drug that FDA would need to review as part of an NDA for an abortifacient indication. At that meeting, FDA received a strong commitment from Dr. Sakiz that he would find a way to bring RU-486 to the U.S. market. Dr. Sakiz stated that Roussel Uclaf would not be directly involved, but instead would work through a third party in the United States. Dr. Sakiz also committed to making the drug available for research on other potential uses. FDA and Roussel Uclaf agreed to continue to work on this matter until remaining issues could be resolved.

At an April 20, 1993 meeting at the FDA, Roussel Uclaf indicated its willingness to modify its 1982 contract with the Population Council, a non-profit scientific and technical organization. These modifications would permit the Population Council and its sublicensees to produce, test, and distribute RU-486 in the United States. The Population Council agreed to work to identify a manufacturer for RU-486 for the United States market and to begin a clinical trial to test the drug in the United States.

At that point, we thought that clinical trials on RU-486 would begin soon in the United States. This proved not to be the case. Before the Population Council would begin clinical trials, the Population Council and Roussel Uclaf undertook complex negotiations pertaining to the transfer of the RU-486 patents and the basis for distribution of the drug in the United States. After a year of these negotiations, on April 14, 1994, the Secretary and senior Department officials met with the heads of Roussel Uclaf and the Population Council.

At that meeting, the parties indicated their willingness to continue their negotiations, and the Secretary made it clear to the negotiating parties that agreement on all outstanding issues should be reached no later than by May 15, 1994.

We are pleased that Roussel Uclaf and the Population Council have concluded their negotiations, and that Roussel Uclaf has donated the patents on RU-486 without remuneration. We anticipate that the Population Council will now pursue the clinical testing of RU-486 in the United States. We will work with the Population Council to make certain that their clinical trials are well-designed and carefully conducted, in order to provide useful information on how the drug might be properly used in this country. We also understand that the Population Council will file a new drug application for RU-486. We will

review it carefully under the appropriate medical and scientific criteria.

It should be recognized that the termination of a pregnancy is not a simple procedure, whether it is done surgically or through a medical regimen. Women should not think that pregnancy termination using a medical regimen will be simple. It will not be. In Europe, where RU-486 has been used in over 150,000 women, the procedure requires several visits to a medical facility, a precise dosing scheme using two different drugs, and close monitoring to care for women who may experience excessive bleeding or other complications. We anticipate that any use of RU-486 in the United States would have to follow the same type of strict distribution and use conditions.

FEB 0 8 1994

The Honorable Ron Wyden
Chairman, Committee on Small Business
Subcommittee on Regulation, Business
Opportunities, and Technology
House of Representatives
Washington, D.C. 20515-6318

Dear Mr. Chairman:

Thank you for your letter regarding the progress in the negotiations between Roussel of France, Hoeschst AG Germany, and the Population Council, for licensing the drug mifepristone (RU-486). We share your concern that continued delays in negotiations delay submission to the Food and Drug Administration (FDA) of an application for marketing approval and the product's availability to American women, assuming it is found to be safe and effective.

As you know, HHS has been working actively with several individuals and organizations in an effort to facilitate the study and potential availability of RU-486 and other antiprogestins in the United States. As you mentioned, the drug is being studied for various possible uses, in addition to abortifacient use.

Our assessment of the current licensing negotiations is that progress is being made. Please be assured that we are following these negotiations closely. We are committed to an expeditious review of the data once a new drug application for RU-486 is submitted to the FDA, so that American women may have access to this alternative to surgical abortion as quickly as possible, if the data show that RU-486 is safe and effective.

Again, thank you for writing on this important public health issue.

Sincerely,

Donna E. Shalala

APPEARS THIS WAY
ON ORIGINAL

cc: HFW-1
HFW-10(2)
HFW-14(2)

R/D: [redacted] HFW-14: 1/6/94
Revised by:
[redacted], HFW-1:1/7/94
[redacted], HF-1:1/10/94
[redacted] GCF-1:1/10/94
[redacted] HFD-500:1/10/94
[redacted] HFD-500:1/10/94
Concur: [redacted] HFD-8:1/10/94
[redacted] HFD-1:1/11/94
[redacted] HF-1:1/11/94
F/T: [redacted]:1/11/94
Retyped per:
[redacted] 01/14/94

S:\WP\ [redacted] RU486WYD
FDA CONTROL NUMBER: 94 1
TRACER #: 64254
OS #: 9312280007

APPEARS THIS WAY
ON ORIGINAL

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103d Congress
United States House of Representatives
Committee on Small Business
Subcommittee on Regulation,
Business Opportunities, and Technology
B-363 Rayburn House Office Building
Washington, DC 20515-6318

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ROBERT LEHMAN
MINORITY SUBCOMMITTEE PROFESSIONAL
202-225-4909

December 22, 1993

The Honorable Donna E. Shalala
Secretary
U.S. Department of Health and
Human Services
Room 615F
Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Madam Secretary:

I know we share an interest in improving both the health and healthcare choices of American women. I strongly endorse the significant initiatives you have launched in this regard. We will work hard to ensure your proposals get the attention and support they deserve during the remainder of the 103rd Congress.

I write to you, today, to urge your action on one element of the evolving healthcare agenda...the U.S. approval and distribution of the French drug RU 486. There have been substantial delays in the still-uncompleted licensing negotiations between the French manufacturer of this important drug, and the U.S.-based Population Council. This, in turn, defers the initiation of clinical trials needed for Food and Drug Administration approval and, ultimately, the drug's availability to American women.

> A clear, personal admonition from you to the negotiating parties at this point, I believe, could do much to overcome final roadblocks to the completion of the licensing agreement.
>
> I strongly urge you to contact executives of the drug manufacturing companies -- Roussel Uclaf of France, and Hoerchst AG Germany -- and request their cooperation.

As you know, RU 486 offers unique properties as an abortifacient and as a varifiable safe alternative to surgical pregnancy termination. And in testimony before this subcommittee, a number of medical researchers have testified that this anti-progestin also may be valuable in treating a number of other conditions and illnesses including endometriosis, Cushing's syndrome, meningioma and perhaps even Alzheimer's disease.

T64254

As one who has fought hard for nearly four years too get a fair and rapid assessment of this drug in the United States, I believe that our government should do all within its power to bring the current negotiations between the manufacturer and the Population Council to a swift and positive conclusion.

The potential benefits of this pharmaceutical...one which we could in the alternative replicate ourselves...are just too promising to ignore, or to be held hostage to the whims of a foreign manufacturer.

Thank you for your attention to this important matter, and for your continuing concern regarding woman's health issues. 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.

Sincerely,

RON WYDEN
Chairman

APPEARS THIS WAY
ON ORIGINAL

9312280007

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

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,

55 Boulevard des Invalides 75340 Paris

JAN 19 1993

The Honorable Ron Wyden
Chairman, Subcommittee on Regulation,
Business Opportunity, and Energy
Committee on Small Business
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is in response to your letter of January 14, 1993, requesting a December 14, 1992, letter from the Food and Drug Administration (FDA) to the President of Roussel-Uclaf and any subsequent reply.

The information requested is enclosed.

It should be emphasized that this correspondence is considered confidential commercial information and is not releasable to the public under the Freedom of Information Act and the FDA's implementing regulations. We request that the Committee not publish or otherwise make public any of the information contained in these documents. We would, of course, be glad to discuss with the Committee staff the confidentiality of any specific document.

Sincerely yours,

Marc J. Scheineson
Associate Commissioner
for Legislative Affairs

Enclosures

cc: HFW-1
HFW-10(3)
HFW-12

cc: The Honorable Jan Meyers
Ranking Minority
cc: Roger McClung

APPEARS THIS WAY
ON ORIGINAL

~~R/D:~~ ——— :1/15/93
R/T: — 1/15/93
F/T: —:1/19/92
CHRM-349 and NO. 12294
(S:\ ——— RU-486.LTR)

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

January 14, 1993

Dr. David Kessler, M.D.
Commissioner
The Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

As you are aware, the Subcommittee on Regulation, Business Opportunities and Energy has been following the development of the drug RU-486 with great interest. Recently, the subcommittee has been particularly interested in whether or not the manufacturer of the drug will move to introduce the drug in the U.S. market.

I read with interest the enclosed copy of a January 12, 1993, editorial in The Wall Street Journal. The editorial mentions a December 14, 1992, letter from you to the President of Roussel/Uclaf, Dr. Edouard Sakiz, wherein the prospects for approval of the drug in the U.S. market are discussed. I request that the subcommittee be provided with a copy of this correspondence and any subsequent reply from Dr. Sakiz or his representative.

As always, the subcommittee appreciates your cooperation and assistance. Should you have any questions regarding this request, please don't hesitate to contact Graydon Forrer of the subcommittee staff at (202)225-7797.

Sincerely,

Ron Wyden

RON WYDEN
Chairman

RW/gjf
enclosure

NOV 14 1996

The Honorable Joe Barton
Chairman, Subcommittee on
Oversight and Investigations
Committee on Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

This is in partial response to your request of September 17, 1996, regarding further information related to the Food and Drug Administration's (FDA) consideration of RU-486 (mifepristone). You raised five issues. As was discussed with Mr. Alan Slobodin of your staff, responses to numbers two and three are enclosed. Answers to the remaining questions and responsive documents will be provided as soon as possible.

Tab A:

- **(2) All unexpurgated books, records (including FOIA requests), correspondence, notes, phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCS or on file servers that are a part of local area or wide area networks) mentioning or pertaining to the July 19, 1996 Reproductive Health Drugs Advisory Committee meeting, including materials related to the individual members of the Advisory Committee, and all materials relating to all ethical issues concerning each member of the Advisory Committee.**

Tab B:

- **(3) All unexpurgated books, records (including FOIA requests), correspondence, notes, phone logs, memoranda, documents (including all drafts and without regard to whether they are on paper or recorded electronically), and electronic mail (irrespective of how stored, including but not limited to those stored on individual PCS or on file servers that are a part of local area or wide area networks) mentioning or pertaining to FDA's consideration of the issue of the possible breast cancer risk factor in connection with RU-486.**

The enclosed documents contain confidential information and other privileged information not releasable to the public under the Freedom of Information regulations promulgated by FDA. We request that the Subcommittee not publish or otherwise make public this information. In addition, given the sensitivity of this issue, as we did previously, we have redacted the names of individuals associated with the clinical trials and application review.

If you have any questions, please advise.

Sincerely,

Sharon Smith Holston
Deputy Commissioner
for External Affairs

Enclosures

cc: The Honorable Thomas J. Bliley, Jr.
Chairman, Committee on Commerce

The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce

The Honorable Ron Klink
Ranking Minority Member
Subcommittee on Oversight
and Investigations

cc: HFW-10 (2)
HFW-1
R/D: [redacted] :11/8/96 ([redacted] \barton\ru.wpd)
Edit: [redacted] :11/14/96
F/T: [redacted] :11/14/96
Control 96-6905

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum

Date 16 July 1996 (Tuesday)

From Executive Secretary

Subject CONFIDENTIAL MATERIAL FOR JULY MEETING

To Members of the Advisory Committee for Reproductive Health Drugs

Attached is the Population Council's safety report on the studies they conducted with mifepristone in the United States.

Please be reminded that this is confidential information.

X Finally, I haven't heard from Lewis, Narrigan, O'Sullivan, Daling, and Azziz concerning the dinner Thursday night at which security and media issues will be discussed. The discussion is scheduled for 7:30 pm in a private dining room and the dinner will start at 8.

Please confirm your attendance at the dinner. (Note my new phone number!)

/S/

Executive Secretary
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED IN PROTOCOL 166A/B

Introduction

This internal Population Council report was generated in preparation for the upcoming Mifepristone NDA 20-687 advisory committee meeting on July 19, 1996. The goal was to summarize all serious adverse events (SAEs) that occurred during the conduct of Protocol 166A/B. SAEs are defined as those events reported to the Council from the clinics which the Council then reported to the FDA on Medwatch forms. All of these SAEs reports have been previously submitted to the FDA in IND 22,047 as well as documented in NDA 20-687.

Results

The data relevant to SAEs have been summarized in the following three tables. Table 1 lists each participating clinic by clinic number, principal investigator name, location and type of clinic. Table 2 identifies, in chronological order of occurrence, each subject for whom a SAE was reported to the FDA on a Medwatch form. The nature of the adverse event(s) is recorded as well as the need for a dilatation and curettage (D&C) or aspiration, intravenous fluids, transfusion or hospitalization. When available, the subject's duration of amenorrhea and ethnicity is provided. Finally, the IND submission number and date the Medwatch form was submitted to the IND are listed.

The summary of Table 2 indicates that a total of 52 subjects had at least one SAE. There was more than one adverse event reported for most subjects on the Medwatch forms. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least 4 subjects are listed in the Summary of Table 2

These serious adverse events resulted in the hospitalization of 26 subjects. Four subjects received transfusions. A total of 28 subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of 34 subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen (15) subjects received methergine or oxytocin for treatment of bleeding, although 11 of these subjects eventually had a surgical procedure.

The Drug Surveillance Department of Roussel Uclaf maintains a database of all serious adverse events associated with mifepristone for any medical use. At the request of Roussel, the Council sends to them information on all SAEs from the U.S. clinical trials that were reported to the FDA. Roussel assigns an "International Drug Surveillance Number" (IDSN) to each SAE and then provides a medical code for the reported SAE. These SAEs from the U.S. trial are thus captured in Roussel's database and are included in their quarterly reports of international SAEsa associated with mifepristone use. The SAEs from the Council's U.S study have been reported in the NDA by this IDSN, in order to correspond to the report numbering system of other SAEs included in our NDA from international use of mifepristone in clinical trials and during post-marketing surveillance. However, this has caused some confusion in identification of subjects in the U.S. clinical trial for three reasons: 1) one subject may be assigned more than one IDSN by Roussel, depending upon how many adverse events occurred, since the IDSN is associated with an adverse event, not a subject; and 2) the medical code for the SAE assigned by Roussel may not precisely correspond to the description of the SAE as reported on the Medwatch form submitted to the FDA by the Council and 3) Roussel has made some mistakes in their coding of subject's identification. The purpose of Table 3 is to clarify the relationship between a subject in the U.S. trial and the IDSN(s) assigned to that subject by Roussel. In Table 3, each subject with an SAE in the Council's trial is identified and the IDSN(s), as assigned by Roussel, that are associated with that subject are listed. The medical code assigned by Roussel for the SAE(s) of each subject is also included.

For four subjects in the U.S. trial, Roussel has not yet assigned an IDSN or medical code (subject 123, clinic 01; subject 076, clinic 03; subject 070, clinic 02; and subject 159, clinic 01). The location in the NDA of the line listing of the SAE, as identified by the IDSN, is also indicated on Table 3. Line listings of all of the SAEs in the U.S. clinical trial were included in either the original NDA submission of March 14, 1996 (Volume 1.66, p. 32) or the NDA Safety Update Report of June 20, 1996 (Volume 3.2, p. 10).

Comparison of U.S. trials and pivotal NDA trials

It is not possible to make a complete comparison of the serious adverse events reported in the U.S. trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the U.S. trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the U.S. and NDA pivotal studies can only be made with the serious adverse events reported from these 52 U.S subjects who had a Medwatch report, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire U.S. database. However, some general comparisons can be made. The total number of subjects enrolled in U.S. Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the U.S. trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by 41 subjects in the U.S. studies who required a Medwatch report. In the NDA pivotal studies, 52 subjects reported metorrhagia or excessive bleeding, which was categorized as severe in 21 subjects However, the manner in which the bleeding was treated differed in the two studies. In the U.S. trials, 32 of the 34 surgical interventions (D&C or aspiration) reported on the Medwatch forms were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of 15 subjects

received surgical interventions for bleeding. The greater number of surgical interventions by U.S. investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the U.S., but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The U.S. investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were 5 cases of hypotension reported on Medwatch forms, although blood pressure readings were given for only 2 of these subjects. There were 7 cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia on the Medwatch forms for U.S. subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported on Medwatch forms of the U.S. subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the U.S. database.

Conclusions

The SAEs reported during the U.S. trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the U.S. trials may be explained by the initial inexperience of U.S. clinicians in providing medical abortion. Investigators in the U.S. trial have indicated that there was a learning curve associated with the treatment of bleeding during the trial The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies. In summary, the current comparison of SAEs between our U S trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of U.S. settings.

Table 1

Clinics in Population Council U.S. Studies Protocol 166A/B

Clinic Number	Investigator Name	Location	Type of Clinic*	Protocol A or B
01				A
02				A
03				A
04				A
05				A
06				A
07		APPEARS THIS WAY ON ORIGINAL		A
08				A
21				B
22				B
23				B
24				B
25				B
26				B
27				B
28				B
29				B

* Other = Clinic or Private Office.

Table 2

IND Safety Reports (Med Watch) Submitted to IND 22,047•

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
C01 (005)	22	Hemorrhage	X		X	X	X	63		107 11/21/94
036	02	Hemorrhage Vomiting Fainting	X		X			44		108 12/01/94
033	02	Vomiting Diarrhea Dehydration			X			49		108 12/01/94
027	02	Hemorrhage Cramping	X			X	X	53		109 12/07/94
042	02	Hemorrhage Cramping Dizziness	X		X		X	51		109 12/07/94
WD (057)	01	Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia	X		X	X		44		110 12/20/94
015	25	Hemorrhage Cramping	X+					46		113 01/18/95
012	25	Hemorrhage Cramping	X					49		113 01/18/95
061	01	Hemorrhage Weak Nausea Pale & Cold			X			57		113 01/18/95
076	02	Hemorrhage Vomiting Cramping Chlamydial infection								113 01/18/95
033	03	Hemorrhage Syncope Pallor	X	X				52		113 01/18/95
022	25	Hemorrhage Cramping Feeling Faint	X		X		X	56		114 01/23/95
050	03	Hemorrhage Dizziness Postural Hypotension (BP 60/ palpable)	X				X	30		114 01/23/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
009	26	Hemorrhage Cramping Syncope	X		X		X	57		115 02/07/95
062	01	Hemorrhage Cramping	X				X	57		118 02/15/95
107	01	Vomiting Dizziness			X					118 02/15/95
114	01	Hemorrhage	X	X			X	62		118 02/15/95
123	01	Hemorrhage Dizziness Headache		X	X			53		118 02/15/95
037	04	Hemorrhage	X		X			65		118 02/15/95
109	01	Hemorrhage Fever	X		X		X	45		119 02/17/95
116	01	Chest Pain					X			119 02/17/95
048	03	Hemorrhage Tachycardia	X				X	51		120 03/03/95
076	03	Hemorrhage Cramping		X						121 03/06/95
060	24	Hemorrhage Hypotension Tachycardia			X	X		54		122 03/10/95
017	23	Hemorrhage Orthostatic Hypotension	X	X	X			57		123 03/13/95
070	02	Gunshot					X			123 03/13/95
030	23	Hemorrhage Syncope Tachycardia Hypotension	X		X			52		124 04/11/95
032	23	Vasovagal reaction			X					124 04/11/95
035	23	Hemorrhage		X	X					124 04/11/95
037	23	Hemorrhage Dizziness Shortness of Breath	X	X	X			51		124 04/11/95
081	26	Hemorrhage Syncope/neck injury	X+				X	51		124 04/11/95
158	02	Hemorrhage Weakness	X	X	X			54		125 04/19/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
159	01	Hemorrhage	X+	X	X			50		125 04/19/95
036	27	Pneumonia					X			132 06/07/95
012	29	Hemorrhage Cramping Faintness	X				X	53		132 06/07/95
028	04	Hemorrhage Dizziness		X						132 06/07/95
075	04	Nausea Dizziness			X					132 06/07/95
004	28	Hemorrhage	X	X			X	55		132 06/07/95
027	28	Hemorrhage Vomiting Lightheaded	X		X		X	50		133 06/13/95
071	23	Hemorrhage Vomiting Dizziness	X		X		X	55		136 07/18/95
030	28	Hemorrhage								136 07/18/95
033	28	Hemorrhage	X				X	46		138 07/25/95
063	28	Anxiety attack Depression Threatened suicide					X	50		139 07/28/95
147	27	Viral meningitis					X			141 08/04/95
074	28	Hemorrhage Passed out	X	X	X		X	60		143 08/09/95
088	28	Hemorrhage (2 Med Watch reports)	X	X	X		X	62		143 08/09/95 144 08/10/95
018	07	Abdominal pain	X					42		145 08/15/95
019	07	Hemorrhage								145 08/15/95
104	28	Hemorrhage Cramping	X	X	X		X	62		146 08/25/95
108	28	Cramping Fever, tender uterus	X	X			X	63		147 09/01/95