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Abortion: Termination of Early Pregnancy with RU-486 (Mifepristone)

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Summary

On September 28, 2000, the Food and Drug Administration (FDA) approved the drug mifepristone, also known as RU-486, for the termination of early pregnancy. In 1988, France became the first country to approve the drug. China and the United Kingdom approved RU-486 in 1991, Sweden in 1992, and the following countries in 1999: Russia, Austria, Belgium, Denmark, Finland, Germany, Greece, Israel, the Netherlands, Spain, and Switzerland. Since 1988, more than 620,000 European women have used the drug to terminate pregnancy. Ten million abortions are performed annually in China, and about half are carried out with RU-486.

Because RU-486 is an abortion agent, the process of moving it out of the lab and into mainstream medicine has been fraught with controversy. Since its discovery, the pro-life movement has been adamantly against the use of this drug for abortion. In the United States, the drug's long journey to FDA approval began in 1983, when the agency agreed to clinical trials of RU-486 sponsored by the Population Council. After many difficulties in finding a manufacturer and distributor for the drug, final FDA approval was granted and the first U.S. orders for RU-486 were shipped on November 20, 2000.

The drug will not be available to women by prescription in pharmacies; instead women will receive it directly in a physician's office. Each woman must be given a *Medication Guide* which explains how to take the drug, who should avoid taking it and what complications may occur. A patient agreement similar to an informed consent document in a clinical trial must be signed. In contrast with surgical abortion, which is completed in minutes, drug induced abortion is more time consuming and uncomfortable. Treatment with RU-486 requires that the patient make three office visits over a 2-week period. Short-term risks associated with the drug are limited: about 1% of women require surgery to stop heavy bleeding and only 0.1% of women in clinical trials required a blood transfusion. To date, there is little evidence of any long term health effects due to use of RU-486.

Nevertheless, legislation introduced in the 107th Congress adds requirements for doctors dispensing RU-486 which, the sponsors state, would provide additional protection for women taking the drug. The bill stipulates that physicians prescribing the drug must meet the following requirements: (1) qualified to handle complications resulting from an incomplete abortion or tubal pregnancy; (2) trained to perform surgical abortions and met all applicable legal requirements to perform such abortions; (3) certified for ultrasound dating of pregnancy and detecting tubal pregnancy; (4) completed a program regarding the prescribing of such drug that uses a curriculum approved by the Secretary of the Department of Health and Human Services (HHS); and (5) have admitting privileges at a hospital located 1 hour or less away from the physician's medical office. In the opinion of pro-choice groups, this legislation represents an unprecedented intrusion into the jurisdiction of FDA and the practice of medicine. They point out that FDA reviewed all the scientific data reflecting the experiences of thousands of women and the agency rejected most of these requirements as medically unnecessary.

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Background

The drug mifepristone, commonly known as RU-486, is a medical or drug-induced alternative to surgical abortion for use in early pregnancy. It was discovered in 1980 by researchers at Roussel Uclaf, a pharmaceutical company jointly owned by the French government and the German company, Hoechst AG. RU-486 belongs to a class of drugs known as antiprogestins. These drugs can prevent or interrupt a pregnancy by blocking the action of progesterone, a naturally occurring hormone. Progesterone allows for the implantation of the embryo and aids in maintaining pregnancy by inhibiting uterine contractions. In early studies, the efficacy of RU-486 as an abortifacient ranged from 60% to 80% when used during the first 7 weeks of pregnancy.[1] Such a rate is too low to be clinically acceptable. However, interest in the drug was greatly increased by a 1985 report which found that efficacy is raised to nearly 100% if administration of RU-486 is followed a few days later by a second type of drug called a prostaglandin, which stimulates uterine contractions.

On September 23, 1988, France became the first country to license RU-486 in combination with a prostaglandin for early abortion. Approval in China and the United Kingdom occurred in 1991, in Sweden in 1992, and in the following countries from 1999: Austria, Belgium, Denmark, Finland, Georgia, Germany, Greece, Israel, Luxembourg, the Netherlands, Norway, Russia, Spain, Switzerland, Taiwan, Tunisia, and Ukraine.[2] According to FDA, since 1988, more than 620,000 European women have used the drug combination to terminate pregnancy. About 5 million abortions annually are carried out in China with RU-486.[3] On September 28, 2000, FDA announced the approval of RU-486 and the prostaglandin misoprostal for use in the United States as an abortifacient in pregnancies of 49 days or less.

The process of moving RU-486 out of the lab and onto the market has been fraught with controversy. In France, Roussel Uclaf suspended distribution of RU-486 on October 26, 1988, in response to threats of boycott and violence from groups opposed to abortion. However, following protests from the public and the medical

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[1]The start of pregnancy is marked from the first day of the last menstrual period (LMP). However, because there are about 2 weeks between when a menstrual period starts and ovulation occurs, 7 weeks pregnant, or 49 days LMP, actually means a 35 day-old embryo.

[2]Christin-Maitre, S., P. Bouchard, and I. M. Spitz. Medical termination of pregnancy. *New England Journal of Medicine*, v. 342, Mar. 30, 2000. p. 946-956; and, personal communication with Sandra Waldman of the Population Council, Feb. 9, 2001.

[3]Pan, P.P. Chinese to make RU-486 for U.S. *Washington Post*, Oct. 12, 2000. p. A1, A18.

community, 2 days later on October 28, 1988, the French Minister of Health Claude Evin ordered RU-486 back on the market, stating that "from the moment governmental approval for the drug was granted, RU-486 became the moral property of women, not just the property of the drug company."[4] At that time, the French government owned 36% of Roussel's stock and therefore was able to exert some influence over company decisions. Also, a 1968 French law gave the health minister the authority to withdraw a company's license to market a drug and award the license to another firm if the company refused to make a drug available.

In the United States, the drug's long journey to FDA approval began in 1983, when the agency agreed to clinical trials of RU-486 conducted at the University of Southern California (USC), under the auspices of the Population Council.[5] More than 300 women received the drug from 1984 until February 1990, when USC researchers exhausted their supply of the drug.[6] USC was unable to obtain more because in 1989 Roussel had made a policy decision not to provide RU-486 for abortion research in the United States. This decision resulted in the drug being used here only in very limited research settings (that did not involve abortion) through arrangements with Roussel.

The Roussel decision was influenced by and came shortly after the June 1989 FDA announcement during the former Bush Administration which placed RU-486 on the import alert list. Import Alert 66-47 (Automatic Detention of Abortifacient Drugs) prohibited the importation of RU-486 into the United States for personal use.[7] The alert was imposed by FDA because of concerns over the drug's possible health risks and use without physician supervision. In general, FDA has the power to prevent the importation of unapproved drugs, and has exercised its authority in a discretionary manner. In 1988 FDA relaxed its rules on importing unapproved drugs for the personal use of those suffering from fatal illnesses like AIDS and cancer.

In July 1992, Leona Benten, a 29-year old pregnant woman, tried to challenge the import ban by bringing into the United States enough RU-486 for her own use. The drug was confiscated on July 1, 1992, by U.S. Customs at New York's JFK airport. Benten filed suit against the FDA and the U.S. Customs Bureau for their enforcement of the import ban. U.S. District Court Judge Charles Sifton heard the case and ruled in her favor on July 14, 1992, finding the FDA policy illegal. Judge

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[4]Klitsch, M. *RU-486: The Science and the Politics*. New York, Alan Guttmacher Institute, 1989.

[5]The Population Council is an international, non-profit research organization established in 1952 by John D. Rockefeller, III to search for a better understanding of problems related to population. The Council conducts research on three fronts: biomedical, social science, and public health. Its mission is to improve the well-being and reproductive health of current and future generations and to help achieve a humane, equitable, and sustainable balance between people and resources. More information at: [http://www.popcouncil.org].

[6]Stephens, T. RU-486 mired in abortion debate. *Journal of NIH Research*, v. 2, Sept. 1990. p. 26-27.

[7]Rovner, J. RU-486: tiny pill with big impact. *Congressional Quarterly*, Feb. 24, 1990. p. 598.

Sifton concluded "the decision to ban the drug was based not from any bona fide concern for the safety of users of the drug, but on political considerations having no place in FDA decisions on health and safety."[8] The decision was stayed hours later by the U.S. Court of Appeals for the Second Circuit. The U.S. Supreme Court agreed to consider an appeal filed by Benten and her attorney, but ultimately the confiscation was upheld by a 7-2 decision on July 17, 1992. The woman subsequently had a surgical abortion.

On January 22, 1993, 2 days after taking office, President Clinton directed Department of Health and Human Services (HHS) Secretary Donna Shalala to: (1) rescind the personal use import ban, barring sufficient evidence to warrant it; and, (2) "assess initiatives" for the promotion of testing, licensing, and manufacturing RU-486.[9] In response to the President's directive, Secretary Shalala published in the *Federal Register* actions to be taken regarding the status of RU-486.[10] The Secretary directed FDA to initiate an immediate and thorough review of the health and safety implications of the potential import of RU-486 for personal use. The findings of the review were to be reported to the Secretary. If there was not enough evidence to limit RU-486 from qualifying as a drug that could be imported for personal use, the import alert would be rescinded.[11] The Secretary also directed FDA to assess promptly initiatives to promote the testing, licensing and manufacturing of RU-486 or other antiprogestins in the United States, and report on options to the Assistant Secretary for Health and the Secretary of HHS.

The change in the Administration's policy on RU-486 generated an increased commercial interest in the drug. According to Roussel, 10 American companies contacted the French firm about manufacturing the drug in the United States.

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[8]Hurtado, P., and P. Moses. Pill's new life: ok by judge but appeals court says no. *Newsday*, July 15, 1992. p. 3.

[9]Presidential Documents. Memorandum of Jan. 22, 1993. Importation of RU-486. *Federal Register*, v. 58, no. 23, Feb. 5, 1993. p. 7459.

[10]Department of Health and Human Services. Office of the Secretary. *Federal Register*, v. 58, no. 23, Feb. 5, 1993. p. 7468.

[11]Import alert 66-47 was cancelled on Sept. 28, 2000, (the day RU-486 received final approval from FDA) and the following paragraph was added to the end of Import Alert 66-41:

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

FDA. Congressional Liaison Office. Personal communication with Joy Stevens. Full text of Import Alert 66-41 can be found at: [www.fda.gov/ora/fiars/ora_import_ia6641.html].

Although it would have preferred enlisting a large pharmaceutical company for U.S. production, only smaller companies and nonprofit agencies came "forward for consideration because of their relative immunity to boycotts on the part of abortion opponents."[12] In April 1993 the Population Council and Roussel announced they had reached a preliminary agreement whereby the company would license the rights for the drug's production to the Council which would conduct a U.S. clinical trial and find a U.S. manufacturer.[13] Roussel agreed to supply RU-486 for the clinical trials. However, the Population Council put its efforts on hold in the fall of 1993 because the two parties were unable to come to a final agreement and sign a contract.[14]

In September 1993, the Institute of Medicine (IOM) released its report, *Clinical Applications of Mifepristone RU-486 and Other Antiprogestins*, funded by the Henry J. Kaiser Family Foundation. Because the drug had been tested extensively in Europe, the IOM panel recommended immediate submission of previous clinical trial data directly to FDA, in lieu of US trials, to determine whether they met U.S. regulatory requirements.[15] The report also recommended aggressive pursuit of research on RU-486 in the treatment of a variety of pregnancy-related conditions and other hormone-linked diseases, such as endometriosis, uterine fibroid tumors, breast cancer, and certain types of brain tumors.[16] However, a citizen petition filed by a pro-life group and signed by several Members of Congress called on the FDA to "strictly review any foreign data submitted for U.S. approval of RU-486."[17]

Following discussions between HHS, the Population Council, and Roussel, on May 16, 1994, the Clinton Administration announced that the company would donate U.S. patent rights for RU-486 to the Population Council.[18] The company agreed to give up potential American profits from sales of the drug reportedly "because of its stated reluctance to market RU-486 in the highly charged U.S. political climate surrounding the issue of abortion."[19] At a congressional hearing, company representative Lester Hyman stated that Roussel originally decided not to seek U.S. approval of the drug because "then-President Bush spoke stridently against any procedure that would result in early pregnancy termination. ... It was only when

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[12]RU-486 distribution plan, physician training would be key elements of U.S. phase III clinical trial. *Blue Sheet*, Mar. 24, 1993. p. 6-7.

[13]Schwartz, J. U.S. group to get rights to produce abortion pill. *Washington Post*, Apr. 21, 1993. p. A1, A5.

[14]RU-486 U.S. status will be reviewed by Rep. Wyden's House Regulations Subcommittee May 16. *Blue Sheet*, Apr. 27, 1994. p. 9-10.

[15]Schwartz, J. Science panel urges FDA to evaluate use of RU-486 abortion pill. *Washington Post*, Sept. 9, 1993. p. A12.

[16]Usdin, S. NAS backs aggressive research on controversial RU-486 drug. *Pharmaceutical Daily*, v. 1, Sept. 8, 1993. p. 1, 4.

[17]Conlan, M. Congressional logic. *Drug Topics*, Mar. 20, 1995. p. 74.

[18]U.S. Congress. House. Committee on Small Business. RU-486, status report on the U.S. commercialization project, transfer of antiprogestin technology to the United States. 103rd Cong., 2nd Sess., May 16, 1994. 48pgs.

[19]Ibid., p. A1.

President Clinton changed the governmental policy and specifically asked Roussel to make the procedure available here, that [Roussel], out of respect for the President of the United States, agreed to make every effort to comply with his request."[20]

From October 1994 to September 1995 the Population Council conducted a U.S. trial of RU-486 involving 2,121 women.[21] The Population Council raised $16 million from other organizations, such as the Open Society and the Kaiser Family Foundation, in order to conduct the trial and prepare the documentation necessary to receive FDA approval.[22] A New Drug Application (NDA) was submitted to FDA on March 18, 1996 by the Population Council seeking approval for RU-486 in combination with the prostaglandin misoprostol. The NDA was based on safety and efficacy data derived primarily from two French trials involving 2,480 women and preliminary data from the U.S. trial. The NDA was classified as a "priority" by FDA because RU-486 was the first drug submitted to the agency for medical abortion.[23]

FDA's Reproductive Health Drugs Advisory Committee evaluated RU-486 and concluded on July 19, 1996, in a 6 to 0 vote (with 2 abstentions) that it is safe and effective as an abortifacient when used under close medical supervision.[24] Although the advisory committee's recommendations are not binding on the agency, FDA generally follows its advice. On September 18, 1996, the FDA issued an approvable letter to the Population Council for RU-486 with misoprostol pending additional information on the manufacturer and the labeling of the drug.[25] An approvable letter is frequently used by FDA to indicate that safety and efficacy data have passed agency review, but additional information needs to be submitted before final approval is granted.

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[20]House Committee on Small Business, RU-486, status report, p. 16.

[21] After the Population Council trial of RU-486 was completed in September 1995, the drug was not available in the United States again until 1997 when a small pro-choice group, Abortion Rights Mobilization (ARM) began conducting their own research trial. ARM developed its own version of the drug and gained FDA approval for its trials in 1996; the manufacturer was a closely guarded secret. ARM made up to 10,000 doses of mifepristone available for research purposes and conducted trials at 15 different sites. Lewin, T. Group is intensifying its campaign to distribute abortion pill. *New York Times*, July 2, 1997. p. A21; and, Joffe, C. Medical abortion and the potential for new abortion providers: a cautionary tale. *Journal of the American Medical Women's Association*, v. 55, supplement 2000. p. 151-154.

[22]Bernstein, S. Persistence brought the abortion pill to U.S. *Los Angeles Times*, Nov. 5, 2000. A1.

[23]Under the Prescription Drug User Fee Act of 1992, P.L. 102-571, priority drugs such as RU-486 have a 6-month goal for initial agency action. *FDA Talk Paper*, Sept. 18, 1996.

[24]The overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. The Committee voted 6-yes and 2-no for data supporting efficacy, and 7-yes and 1-abstention for data supporting safety. FDA memorandum to the Population Council, Sept. 28, 2000.

[25]Bachorik, L. FDA issued approvable letter for mifepristone. *FDA Talk Paper*, Sept. 18, 1996. For more information on the approvable letter, see 21 CFR 314.110.

Some predicted that RU-486 would become generally available in the United States by mid-1997.[26] However, the Population Council "had a number of difficulties in finding an appropriate manufacturer and distributor for the drug, in part because of the reluctance of established pharmaceutical firms to enter into such a controversial and potentially violent arena."[27] [28] Because of continued fear on the part of investors and manufacturers of being targeted by pro-life groups, the Population Council apparently found it necessary "to set up elaborate consortiums and front groups to protect participants, to the point of using cumbrous and ultimately unworkable arrangements."[29] A Hungarian company, Gedeon Richter, agreed to produce the drug for the Population Council in 1995, but backed out of the agreement in February 1997; the dispute ended in a breach of contract lawsuit.[30] Although fear of boycotts and violence may have deterred some manufacturers from becoming involved in manufacturing RU-486, others speculate, including some pro-life groups, that the companies also feared the costs of potential product liability litigation.[31]

In April 1996, 1 month after filing the RU-486 NDA with FDA, the Population Council granted to Advances in Health Technology (AHT) exclusive legal rights to arrange for and coordinate U.S. manufacture and distribution of RU-486. AHT was a nonprofit organization formed by the Population Council in late 1995.[32] Almost a

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[26]RU-486 decision a milestone in abortion rights effort. *Los Angeles Times*, Sept. 20, 1996. p. A10.

[27]Joffe, C. Medical abortion in social context. *American Journal of Obstetrics and Gynecology*, v. 183, Aug. 2000 supplement. p. S10-S15.

[28]The National Abortion Federation tracks clinic violence statistics by year and maintains a chronological history of murder/shootings and arson/bombings that have occurred at abortion clinics. Click on *Clinic Violence* at: [www.prochoice.org/]. In addition, the Feminist Majority Foundation provides information on clinic violence at: [www.feminist.org/rrights/abrights_links.html#violence].

[29]Safe drug, no sales. *Washington Post*, May 18, 1998. p. A16.

[30]Murphy, C. Abortion pill's U.S. sponsor suing Hungarian drug firm. *Washington Post*, June 12, 1997. p. A3.

[31]Wills, S.E. *RU-486: Coming to America?* National Conference of Catholic Bishops. Life Issues Forum, Sept. 15, 2000.
At: [www.nccbuscc.org/prolife/publicat/lifeissues/09152000.htm

[32]While the approval process for RU-486 has been complicated by the opposition of pro-life groups, the Population Council also experienced another unrelated delay. Between the end of 1996 and early 1997, the Population Council was distracted by a court case involving a lawyer/investor named Joseph D. Pike. On November 4, 1996, the Population Council and AHT filed a complaint in New York Superior Court against Mr. Pike, a lawyer selected by the Population Council in 1995 to raise funds needed to market, manufacture and distribute RU-486. Media reported that the complaint charged Pike with fraud for withholding information on his 1993 disbarment and a May 1996 conviction, both of which stemmed from 1985 real estate deal in North Carolina. The Population Council and AHT sought to remove Pike from control of the license to market RU-486 and appoint a court-ordered receiver with authority to sell all stock owned by Pike to acceptable third parties. By 1996, Pike was said to have raised more than $27 million for the RU-486 project, including $6 million of his own

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year later, AHT's functions were merged into Advances for Choice, and the new company was to be responsible for marketing and distributing RU-486 for the termination of early pregnancy as well as development of the drug for other medical conditions. However, the company name changed several times from Advances for Choice to Advances/Neogen, and then finally to Danco Laboratories LLC, with some management and investor switches along the way.[33] Danco currently is the Population Council's sublicensee responsible for marketing RU-486 in the United States. Danco and the Population Council received financial assistance, in the form of grants and loans, from foundations set up by investor George Soros (the Open Society), investor Warren Buffet (the Buffet Foundation), and co-founder of Hewlett-Packard, David Packard (the David and Lucille Packard Foundation).[34]

Meanwhile, the prospects for RU-486 remaining an abortion option for women in Europe also began to look uncertain. On April 8, 1997, the German company, Hoechst announced that it would cease production of RU-486.[35] The decision was influenced by a pro-life group boycott of the company's new (and potentially far more lucrative) allergy drug, Allegra. Roussel, now fully owned by Hoechst, was directed to transfer the patent rights and the remaining stockpile of RU-486 to a new company headed by Roussel's former chief executive, Dr. Edouard Sakiz. Dr. Sakiz was also on the team of scientists that had originally developed the drug. The new company, Exelgyn, would continue to provide RU-486 in Europe; however, without a manufacturing facility, the stockpile was predicted to run out by the end of 1998. Strict guidelines developed by Roussel had effectively limited the drug to France, the UK and Sweden and legal requirements confined abortion services to residents of those three countries. Attempts to expand the drug's distribution to other countries had been hampered by Roussel's highly unusual demand that "a government must issue a formal request...and secure means of distribution and quality follow-up care must be provided."[36] Exelgyn planned to introduce RU-486 in several more European countries and make it available to researchers examining other uses of the drug. However, like Danco, Exelgyn had great difficulty finding a manufacturer; several large companies refused, due to concern over potential violence from groups opposed

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[32](...continued)
funds. Although a trial was scheduled for March 31, 1997, the Population Council announced on February 12, 1997 that the litigation had been settled and that Pike had sold a "substantial portion" of his equity to a new company, Advances for Choice. Murphy, C., and K. Day. Abortion pill's U.S. debut snagged by business dispute. *Washington Post*, Jan. 12, 1997. p. A1, A18, A19; Lewin, T. Lawsuits' settlement brings hope for abortion pill. *New York Times*, Nov. 13, 1997. p. A14; Bernstein, S. Persistence brought the abortion pill to U.S. *Los Angeles Times*, Nov. 5, 2000. p. A1; and, Murphy, C. Abortion pill accord clears way for sales. *Washington Post*, Feb. 13, 1997. p. A1, A15.

[33] RU-486 action date is Sept. 30; Allen named Reproductive Division Director. *Pink Sheet*, June 12, 2000. p. 14.

[34] Zimmerman, R. Choice allies: awaiting green light, abortion-pill venture keeps to the shadows. *Wall Street Journal*, Sept. 5, 2000. p. A1.

[35]Schuman, J. Firm gives up rights to RU-486. *Washington Post*, Apr. 9, 1997. p. C12.

[36]Medical and health news: Roussel-Uclaf to transfer RU-486 rights. *Reproductive Freedom News*, v. 6, Apr. 18, 1997. p. 8.

to abortion. By early 1998, Exelgyn had found manufacturing partners but refused to identify them publicly.[37] RU-486 was approved for use by a number of other European countries in 1999.[38]

In early June 2000, the FDA offered in a letter to the Population Council and Danco a proposal for allowing the drug to be marketed so long as the following conditions were met: (1) a national registry of all physicians prescribing RU-486 would be established by Danco; (2) all physicians on the registry would have admitting privileges at a hospital within 1 hour of their offices; (3) only physicians trained in providing surgical abortions would be allowed to prescribe RU-486; (4) physicians would have to be trained in using RU-486; (5) physicians would have to be trained in reading ultrasound scans; and, (6) a follow up study of all women who have had medical abortions would be conducted by the Population Council.[39] A spokesperson for the Population Council indicated that the FDA proposal was "more restricted than we had expected."[40] [41] Pro-life groups believed that the agency's proposal was prudent, and should be strengthened even further.[42]

Pro-choice advocates were alarmed at the FDA proposal, particularly with the national registry which might cause physicians prescribing RU-486 to become a target for violence by groups opposed to abortion. In a *Washington Post* article, Gloria Feldt, president of the Planned Parenthood Federation of America, stated that the FDA proposal "would so violate physicians' privacy and security concerns that [RU-486] could be approved by the agency but never really be on the market."[43] In the same article, Paul Blumenthal, medical director of Planned Parenthood of Maryland, stated that FDA was making unprecedented demands on physicians prescribing RU-486. According to Blumenthal, "what they have recommended in terms of the kind of certification and licensing of providers before they can provide the drug is beyond what they do with any other drug. ... [It] certainly seems that a different standard is being used for [RU-486]."[44] Generally, FDA either approves or does not approve a drug, and only rarely does the agency place restrictions on how a drug can be used by doctors. Lars Noah, a University of Florida law professor who specializes in FDA

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[37]Scientist has maker for RU-486 but says issue still sensitive. *Associated Press*, Feb. 13, 1998.

[38]See footnote 2.

[39]Kaufman, M. Abortion drug proposal criticized. *Washington Post*, June 7, 2000. p. A1, A8; and, Stolberg, S.G. FDA adds hurdles in approval of abortion pill. *New York Times*, June 7, 2000. p. A21.

[40]Ibid.

[41]However, at the time of the July 1996 advisory committee review of RU-486, the Population Council stated it planned to distribute the pregnancy termination pill only to physicians trained in surgical abortion, and AHT stated it would offer training in surgical abortion to facilitate availability of the product. *Pink Sheet*, June 12, 2000. p. 14.

[42]Zimmerman, R. Abortion-rights leaders fight FDA limits on RU-486. *Wall Street Journal*, June 13, 2000. p. B6.

[43]Kaufman, Abortion drug proposal criticized, p. A8.

[44]Ibid.

issues, could only identify two cases in which severe restrictions were placed on the use of a drug, Acutane (acne drug) and thalidomide (AIDS and leprosy treatment), both because of the risk of birth defects.[45]

Abortion rights advocates were also concerned about requiring that only physicians trained in providing surgical abortions be allowed to prescribe RU-486. The number of physicians trained in performing surgical abortion has been steadily declining.[46] Many attribute the decline to terrorism from groups opposed to abortion. Pro-choice advocates, on the other hand, agreed with FDA that "providers need specific training in how to administer the drug, counsel patients on its use and provide surgical backup in case there are complications or the drug fails to work, which happens in 5% of cases."[47]

A second approvable letter had been issued by FDA to Danco on February 18, 2000, that addressed labeling, manufacturing, chemistry and distribution issues. Danco had responded to the second letter at the end of March 2000.[48] Because RU-486 is a Class 2 submission requiring substantial review work, according to guidelines in the Prescription Drug User Fee Act, a response must be made by FDA within 6 months. This requirement resulted in an agency action deadline of September 30, 2000.[49]

FDA Approval of RU-486

Two days before its deadline (see above), on September 28, 2000, FDA announced the approval of RU-486 in combination with misoprostol for the termination of early pregnancy, which was defined as 49 days or less counting from the beginning of the last menstrual period.[50] Mifeprex is the trademark of Danco Laboratories; company literature also refers to the drug as "The Early Option Pill."[51] The cost of the Mifeprex is expected to be around $300, about the same as a surgical abortion. The drug will not be dispensed to women by prescription in pharmacies. Instead women will receive Mifeprex directly in a physician's office, and it must be administered in the presence of a health professional. The physician must be able to determine accurately the duration of the pregnancy from (menstrual history and clinical examination) and must be able to diagnose an ectopic (tubal) pregnancy. Each woman receiving the drug must be given a *Medication Guide* which explains how to

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[45]Marbella, J. FDA fuels abortion pill debate. *Baltimore Sun*, June 12, 2000. p. 1A.

[46]Abortion providers decrease 14% between 1992 and 1996. News Release, Alan Guttmacher Institute, Dec. 11, 1998.

[47]Mann, J. We need the abortion pill now. *Washington Post*, June 23, 2000. p. C9.

[48]Searle *Cytotec* pregnancy reminder issued as RU-486 action nears. *Pink Sheet*, Aug. 28, 2000, p. 14.

[49]RU-486 action date is Sept. 30,*Pink Sheet*, p. 14.

[50]For more information, including the FDA Press Release, mifepristone label, and approval letter, see the FDA website [www.fda.gov/cder/drug/infopage/mifepristone/].

[51]Danco has opened a toll-free telephone number at 1-877-4-Early Option (1-877-432-7596) and a website [www.earlyoptionpill.com] to provide information about mifepristone.

take the drug, who should avoid taking it, and what complications may occur. The physician and the patient must sign a patient agreement similar to an informed consent document in a clinical trial.

Most of the restrictions proposed by FDA in the June 2000 letter to Danco were not included as part of the final approval. There will be no registry of doctors prescribing the drug or special certification program. Prescribing doctors will not be required to be trained in performing surgical abortions, nor be required to have admitting privileges at a hospital within 1 hour of their offices. However, prescribing doctors must be prepared to refer the patient to another trained individual in case of incomplete abortion. Although the FDA Label states that ultrasound should be used if the duration of pregnancy is uncertain or if a ectopic pregnancy is suspected, the physician need not be trained in ultrasound and may refer the patient elsewhere if an ultrasound scan is needed in his medical judgement.

Randall K. O'Bannon, Ph.D., Director of Education and Research at the National Right to Life Committee (NRLC), believes that FDA "modified or set aside many of the patient protections" contained in the June 2000 FDA letter "under pressure from pro-abortion groups and many of their sympathizers in the medical establishment."[52] O'Bannon is of the opinion that "giving a woman RU-486 without giving her an ultrasound thus invites futility, if not outright disaster, if a doctor miscalculates the length of a woman's pregnancy or fails to eliminate the possibility of a tubal pregnancy."[53] According to CDC data, 2% of pregnancies in the United States are ectopic.[54] However, "the reported rate of ectopic pregnancy among women who seek early abortion is much lower" for unknown reasons.[55]

The post-marketing studies mentioned in the June 2000 FDA letter will be conducted by the Population Council. These will include: (1) a comparison of patient outcomes among physicians who refer their patients needing surgical intervention to those who perform the procedure themselves; (2) an audit of prescribers that will examine whether doctors and patients are signing the patient agreement form and filing it in the patient's medical record as required; and, (3) a system for surveillance, reporting and tracking rare ongoing pregnancies after treatment with RU-486 in the United States.[56]

If a significant degree of adverse events or problems are found in the post-marketing studies, individual doctors could lose their prescribing rights for this drug and the overall approval could be reexamined. The media has speculated that this requirement "could make the drug more easily withdrawn under a new

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[52]O'Bannon, R.K. Proposed bill would reinstate safeguards for women taking RU-486, Feb. 8, 2001. At: [www.nrlc.org/RU486/safegardbill.html].

[53]Ibid.

[54]Ectopic pregnancy – United States, 1990-1992. *MMWR*, v. 44, Jan. 27, 1995. p. 46-48.

[55]Kruse, B., et al. Management of side effects and complications in medical abortion. *American Journal of Obstetrics and Gynecology*, v. 183, Aug. 2000 supplement. p. S65-75.

[56]FDA approves RU-486 with several risk management measures. *FDA Week*, Sept. 29, 2000. p. 7-8.

administration. ... Republican leaders have made clear they want to overturn the decision, and House Republican Conference Chairman J.C. Watts said that 'a new administration, I am certain, with moral leadership and a commitment to the family will reverse this Clinton-Gore decision.'"[57]

In contrast with surgical abortion, which is completed in minutes, medical abortion is more time consuming, somewhat like a natural miscarriage. Treatment with Mifeprex and misoprostal requires that the patient make three office visits over a 2-week period. On *day 1*, the patient reads the *Medication Guide*, reads and signs the *patient agreement*, and then swallows three tablets of Mifeprex in the presence of a health professional. Some women do not experience any physical discomfort after taking the drug while others experience light uterine bleeding. The side effects of Mifeprex are similar to "morning sickness" of a normal pregnancy: nausea, headache, weakness and fatigue.

On *day 3*, the patient returns to the office and is examined to determine if she is still pregnant.[58] If pregnant, she will be given two tablets of misoprostol. Side effects are more commonly experienced after taking misoprostol, including nausea, vomiting and diarrhea. Abdominal cramps are a normal and expected part of the abortion process. In the U.S. trials, 96% of women experienced cramping; in the French trials, 83% of women experienced cramping. The pain can be severe and last for several hours. Bleeding and spotting will occur for an average of 9-16 days. According to the FDA and the Population Council, in about 1 out of 100 women, surgery is required to stop heavy bleeding. Serious bleeding requiring blood transfusion can occur but is very rare; only 38 women received transfusions of a total of 25,907 (0.1%) in clinical trials of mifepristone with misoprostol.[59]

On *day 14*, the patient has a follow-up visit to confirm the pregnancy has been terminated and assess the level of bleeding. Although researchers have been experimenting with different dosages and reduced doctor visits since the approval of September 18, 1996, FDA "will not allow divergences from the approved protocol and doctors who use different protocols could lose their ability to order the drug."[60]

According to FDA, since 1988 more than 620,000 women in Europe have taken RU-486. RU-486 is given up to the 49th day of pregnancy in most countries; in Sweden and the UK, RU-486 is given up to the 63rd day in combination with gemeprost, a prostaglandin in vaginal suppository form. RU-486 is less effective later in pregnancy because the placenta begins to produce progesterone in larger amounts by the 10th week of pregnancy, and therefore antiprogestins like RU-486 are unable to compete with the natural hormone. In France, both injectable and suppository forms of prostaglandins were used initially. However, since May 1992 oral prostaglandin has been used in France instead of the injectable form because there

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[57]Kaufman, M. FDA approves abortion pill. *Washington Post*, Sept. 29, 2000. p. A1, A18.

[58]Only 2% to 5% of patients abort with mifepristone alone. *Medical Letter*, Oct. 30, 2000. p. 101.

[59]Christin-Maitre, Medical termination of pregnancy, p. 951.

[60]Kaufman, FDA approves abortion pill, p. A1, A18.

were a few serious cardiovascular complications (including one fatal heart attack in 1991) during medical abortions following the use of the injectable prostaglandin (suprostone).[61] The complications were most often associated with patients who were heavy smokers.

The Mifeprex labeling warns that it should not be used in women with the following conditions:

- ectopic (tubal) pregnancy;
- intrauterine device in place;
- chronic failure of adrenal glands;
- current long-term therapy with corticosteroids (anti-inflammatory);
- allergy to RU-486, misoprostal or other prostaglandins; and
- bleeding disorders or current anticoagulant (blood-thinning) therapy.

According to the Population Council, there is little evidence of any long-term health effects due to use of RU-486.[62] Risk is very small because the drug causes very few side effects, exposure is brief, dosage is small, and most of the drug is eliminated from the body within 2 to 3 days. The oral prostaglandin misoprostol has been used safely for gastric ulcers for many years, and the small dosage taken following the use of RU-486 is much less than the daily dose taken by those who use the drug for ulcers. There are no indications that treatment with RU-486 and misoprostol will cause fetal deformities.[63] Nor is there evidence that the treatment will affect a woman's future fertility. However, pro-life groups claim that the use of RU-486 carries risks and doctors and women need to be made aware of the risks. American Life League President Judith Brown states that "grass-roots people have to be encouraged to identify who these physicians are who are going to distribute this drug, and then try to educate them about the problems."[64]

Reportedly, due to fears of potential violence by abortion opponents, FDA, for the first time, did not publish the names of the experts who reviewed RU-486 for the agency, nor did it publish the name or location of the company that will manufacture the drug.[65] An article in the *Washington Post* identified the manufacturer as Hua Lian Pharmaceuticals located near Shanghai.[66] RU-486 will be shipped in bulk amounts in powder form to another factory, possibly in the U.S., in order to be formulated into

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[61]Population Council. *Frequently Asked Questions, Medical Abortion, Mifepristone and Misoprostol.* [www.popcouncil.org/faqs/abortion.html]

[62]Ibid.

[63] In Europe, of 71cases studied of continuing pregnancy (woman changes her mind after starting treatment or doctor fails to follow up), eight malformations were reported. Five were discovered in pregnancy and led to therapeutic abortion, and three were found at birth. All cases of malformation occurred with mifepristone alone (one case) or with the prostaglandin gemeprost (seven cases). No cases of malformation were associated with use of mifepristone and misoprostol. Sirruk-Ware, R., et al. Fetal malformation and failed medical termination of pregnancy. *Lancet*, v. 352, July 25, 1998. p. 323.

[64]Toner, R. A tactical challenge. *New York Times*, Sept. 29, 2000. p. 10.

[65]Kaufman, FDA approves abortion pill, p. A1, A18.

[66]Pan, Chinese to make RU-486 for U.S., A18.

200mg pills. Hua Lian has been making the drug for 9 years, one of three Chinese companies that has been manufacturing RU-486 under different brand names for use in China. The *Washington Post* article said that 10 million abortions are performed annually in China, and about half are carried out with RU-486 citing the director of the Shanghai Institute of Planned Parenthood Research.[67] Hua Lian "has been working for three years to upgrade its equipment and retrain its staff to meet international standards in order to be permitted to export the drug."[68] The company received assistance from the Rockefeller Foundation and the Bangkok-based Concept Foundation in this effort to upgrade its factory.[69]

In a press release dated October 12, 2000, NRLC legislative director Douglas Johnson expressed concern over the importation of RU-486 from Hua Lian. "It is a public health issue because China is a major source of impure drugs – and the FDA cannot possibly monitor a Chinese factory effectively. It is a human rights issue because Hua Lian Pharmaceutical is a major component of the Chinese government's population control program, which relies heavily on compulsory abortion."[70] The NRLC's Randall O'Bannon believes the Chinese manufacturer of RU-486 is "problematic" for two reasons. "First, the Chinese developed their version of the abortion pill in the 1980s after copying the pill produced by the French. Whether this has the same chemical formula, whether it has the same level of safety and effectiveness as the French pill, whether it has the same risks and provokes the same side effects, or worse, is not clear. Second, another huge challenge would be the ability of Danco and FDA to monitor the production process in a distant, totalitarian country, with a notorious human rights record, particularly when it comes to state-mandated abortions and sterilizations."[71]

The House Commerce Committee raised questions about Hua Lian in a letter to FDA concerning the company previously being "cited by federal regulators for bringing mislabeled and impure drugs into the United States."[72] According to an FDA spokesperson, "As with all drugs the FDA approves, in the case of mifepristone, the FDA throughly inspected its manufacturer and the facility passed. It fully met the FDA's standards."[73] According to an FDA memorandum to the Population Council,

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[67]Ibid.

[68]Ibid.

[69]Ibid.

[70]Abortion drug will be imported from Chinese government factory that plays key role in population-control program, Oct. 12, 2000.
At: [www.nrlc.org/press_releases_arc/Release101200.html].

[71]O'Bannon, R.K. *Made in China?* At: [www.nrlc.org/RU486/china/html].

[72]Zitner, A. RU-486 firm linked to drug impurities. *Los Angeles Times*, Oct. 20, 2000. p. A1.

[73]Ibid.

that inspection took place on July 24-28, 2000; "Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable."[74]

Although the FDA Commissioner who presided over the approval of RU-486, Dr. Jane E. Henney, indicated her interest in staying on with the agency, her resignation was accepted by the incoming Administration.[75] [76] At his Senate confirmation hearing, then Wisconsin Governor Tommy G. Thompson, the Bush appointee for Secretary of HHS, indicated that "he would conduct a new review of the safety of the abortion drug RU-486."[77] Mr. Thompson stated that the approval of the drug "was contentious, was controversial," however, he also stated that he did "not intend to roll back anything unless it is proven to be unsafe. ... I don't know the specifics, people have told me there are some safety concerns. If there are, we want to review them."[78]

Potential Impact of RU-486

Danco began shipping the first orders for RU-486 on November 20, 2000.[79] Planned Parenthood, a family planning group that supports abortion rights, stated that about 60 of its clinics would begin offering the drug that same week.[80] Activists on both sides of the abortion debate have recognized that RU-486 could fundamentally change the struggle by allowing women to obtain "abortions in many more doctors' offices and clinics, making the procedure much more widely available and private."[81] Gloria Feldt, president of Planned Parenthood Federation of America, has stated that the approval "is an historic moment, comparable to the arrival of the birth control pill 40 years ago."[82] According to Judith Brown, president of the American Life League, "Mifepristone will absolutely make our battle harder to fight and harder to win."[83]

Pro-life groups are concerned about the approval of RU-486 because of their larger concerns over abortion and the sanctity of life. In response to the FDA approval, the National Conference of Catholic Bishops commented that "approving chemical abortion will further numb our consciences to the violence of abortion and

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[74]U.S. Department of Health and Human Services. Public Health Service. Food and Drug Administration. Center for Drug Evaluation and Research. Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council. September 28, 2000.

[75]Henney calls FDA commissioner "best job;" low-key bid to stay is long shot. *Pink Sheet*, Dec. 18, 2000. p. 26.

[76] Pear, R. Thompson says he will order a new review of abortion drug. *New York Times*, Jan. 20, 2001. p. A11.

[77]Ibid.

[78]Ibid.

[79]Associated Press. RU-486 is shipped to clinics, doctors. *Newsday*, Nov. 21, 2000. p. A44.

[80]First shipments of RU-486 head to doctors. *St. Louis Post-Dispatch*, Nov. 21, 2000. p. A5.

[81]Kaufman, M. Abortion pill deliveries begin soon. *Washington Post*, Nov. 16, 2000. p. A2.

[82]Kaufman, FDA approves abortion pill, p. A1.

[83]Pill alters abortion debate. *Christian Century*, Jan. 26, 2000. p. 84-85.

the taking of innocent human life."[84] Although pro-life groups have some specific concerns about the safety of the drug for women, their more general concern is that RU-486 is another abortion procedure that will be used to end the life of the unborn. In the opinion of the NRLC, "chemical abortions, like RU-486, give supporters of abortion a chance to change the image of abortion, making it seem as simple as taking a pill and concentrating on smaller, less developed babies whose destruction seems an easier political sell. That the reality is far different – that these abortions offer a whole new set of significant risks, that the objective is still the destruction of a unique human life – is of little consequence to abortion's promoters as long as their false perception holds."[85]

Furthermore, pro-life groups are concerned that RU-486 will increase the number of abortions performed in this country. In response to the FDA approval, then Texas Governor George W. Bush reportedly stated his concern that RU-486 would make abortions "more and more common rather than more and more rare."[86] However, other observers have concluded that "the availability of medical abortion in France, England and Sweden has not increased the number of abortions overall in those countries."[87] According to pro-choice advocates, the impact of RU-486 in the United States is expected to be the same as in Europe, and a decline in abortions in the United States is expected to continue.

According to the Centers for Disease Control and Prevention (CDC) the annual number of abortions in the United States has been falling for a variety of reasons, including the demographics of the U.S. female population (aging baby boomers), the passage of abortion laws affecting adolescents (requiring parental consent) and increased use by adolescents of condoms and long-acting hormonal contraceptives.[88] From 1990 (the year in which the number of abortions was highest) through 1995, the annual number of abortions in the United States decreased by 15%. From 1995 to 1996, the number of abortions increased slightly by 0.9%, and in 1997, the number of abortions declined again by 3%. The number of abortions reported to CDC for 1997 was 1,186,039, the lowest recorded number since 1978.[89]

Proponents of RU-486 also argue that it could help shift abortions to an earlier stage within the first trimester, the first 12 weeks of pregnancy. Polling data indicate

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[84]United States Catholic Conference. National Conference of Catholic Bishops. Bishops conference official comments on approval of abortion pill. Sept. 28, 2000. At: [www.nccbuscc.org/comm/archives/2000/00-243.htm].

[85]RU-486: the pill, the process, the problems. At: [www.nrlc.org/RU486/ru486all.html].

[86]Kaufman, FDA approves abortion pill, p. A18.

[87]Talbot, M. The little white bombshell. *New York Times Magazine*, July 11, 1999. p. 39-43, 48, 61-63.

[88]Centers for Disease Control and Prevention. CDC Surveillance Summaries, Dec. 8, 2000. *MMWR 2000*, v. 49. 44 p.

[89]Ibid.

that early abortions are "more politically tenable."[90] A March 30-April 2, 2000, Gallup poll found that 65% of Americans think abortion should be legal in the first 3 months of pregnancy, and 50% favor the FDA decision to make RU-486 available in the United States.[91] According to CDC data, in 1997, 88% of abortions were performed before 13 weeks; 55% were performed at 8 weeks or earlier.[92] With the increased use of at-home pregnancy tests, women are requesting abortion services as early as the fourth week. Some clinicians have been reluctant to perform a surgical abortion before the eighth week because the size of the embryo is so small, it could be missed during the abortion procedure which uses a suction tube device to remove the embryo from the uterus. It is standard procedure for the doctor to inspect the tissue removed during an abortion in order to confirm that the pregnancy has been terminated. Identification of the gestational sac, which contains the embryo, can be more difficult at the very early stages of pregnancy. However, a combination of increased use by doctors of: (1) medical abortion via RU-486; and (2) newer surgical techniques used with ultrasound to confirm early pregnancy termination, may shift the timing of when many abortions are performed to between the fourth and the seventh week of pregnancy.

Pro-choice groups hope that RU-486 will improve access to abortion services by reversing the steady decline in the number of physicians and clinics offering such services. According to research conducted by the Alan Guttmacher Institute (AGI), the number of abortion providers in the United States began to declined in the 1980s. In its most recent survey, AGI found that between 1992 and 1996, the number of providers fell 14%.[93] In 1996, 86% of U.S. counties lacked abortion services and 32% of women of reproductive age lived in counties with no provider.[94] The Institute found that many nonmetropolitan areas particularly lack such services; "95% of such counties had no abortion services and 87% of nonmetropolitan women lived in unserved counties."[95] Members of the pro-choice movement attribute the continued decline in abortion providers to ongoing harassment and violence from groups opposed to abortion. Pro-choice leaders believe that if more physicians quietly began offering RU-486 in their private offices, this may reduce the potential for violence associated with abortion provision by greatly increasing the number of sites where such services are available and by making these sites more dispersed and less publicly identified with abortion.

Surveys examining the intentions of doctors from various specialties to provide medical abortion using RU-486 have found that many are considering offering the

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[90]Talbot, The little white bombshell, p. 41.

[91]Gallup Organization. *Abortion Issues*. [www.gallup.com/poll/indicators/indabortion.asp]

[92]Centers for Disease Control and Prevention; *MMWR 2000*.

[93]Henshaw, S. Abortion incidence and services in the United States, 1995-1996. *Family Planning Perspectives*, v. 30, Nov./Dec. 1998. p. 263-270.

[94]Ibid.

[95]Ibid.

drug to their patients.[96] [97] A survey conducted by the Henry J. Kaiser Family Foundation from January 19-April 27, 2000, found that 44% of gynecologists and 31% of family practice physicians were very or somewhat likely to prescribe RU-486.[98] According to the Kaiser survey, those most likely to offer RU-486 are the 26% of gynecologists who routinely or occasionally perform abortions: 79% of these doctors said they would offer the drug. "Of particular note are those providers who have never or not within the last five years performed a surgical abortion: 31% of gynecologists who fall in this group (72% of all gynecologists) say they are at least somewhat likely to prescribe mifepristone, as are 31% of family practice physicians, the large majority of whom (98%) do not perform abortions."[99] However, of those interested in providing RU-486, major deterrents would be the need for: (1) additional malpractice insurance; and (2) completion of certified training program and requirement that FDA labeling be followed exactly.

In 2000, the National Abortion Federation reportedly trained over 2,000 doctors and health care professionals on how to use RU-486; 25% of those trained were not currently providing abortion services.[100] If orders received by Danco for RU-486 are any indication, however, interest in prescribing by doctors not currently providing abortion has not yet materialized. According to a Danco spokesperson, "most of the orders are from Planned Parenthood or independent abortion clinics."[101] A recent *New York Times* article stated that "while in theory, at least, any licensed doctor could offer mifepristone, many say now that they have no intention of doing so and others say they will try to avoid providing the drug."[102]

Some doctors will decide against dispensing RU-486 because they have moral objections to providing any form of abortion. Additional reasons for the doctors' position on the drug include: the risk of being picketed or shunned by the community; the prolonged amount of time it takes to provide a mifepristone abortion; and, the

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[96] A 1996 survey of doctors belonging to the Society for Adolescent Medicine found that 42% would prescribe legal medical abortion; only 2% were offering surgical abortion at the time of the survey. Miller, N., et al. Attitudes of the physician membership of the Society for Adolescent Medicine toward medical abortion for adolescents. *Pediatrics*, v. 101, May 1998. [www.pediatrics.org/cgi/content/full/101/5/e4]

[97] A 1994 survey of doctors practicing in small communities in Idaho found that 26% would definitely prescribe RU-486 and 35% were uncertain. Although a majority of the doctors in the study refused to perform a surgical abortion, almost half said they currently are prescribing the *morning after pill*. The study was funded by the U.S. Public Health Service. Rosenblatt, R., et al. Abortion in rural Idaho: physicians' attitudes and practices. *American Journal of Public Health*, v. 85, Oct. 1995. p. 1423-1425.

[98] Henry J. Kaiser Family Foundation. *Views of Women's Health Care Providers on Abortion: An Update on Mifepristone, and What Happens after FDA Approval*. Menlo Park, CA, June 2000. 19 p. A total of 767 physicians were surveyed.

[99] Ibid., p. 2-3.

[100] Kaufman, Abortion pill deliveries begin soon, p. A2.

[101] Kolata, G. Wary doctors spurn new abortion pill. *New York Times*, Nov. 14, 2000. p. F1.

[102] Ibid.

expensive ($27,000) ultrasound equipment needed to check on the status of early pregnancy.[103] Other potential constraints are the numerous state laws regulating doctors who perform abortions. Proponents of these state laws believe they provide useful protection for women undergoing abortion while opponents feel that many of the laws are a thinly veiled attempt to restrict and discourage access to abortion. These state laws cover such topics as: reporting requirements; informed consent and waiting periods; drug dispensing authority; parental notification or consent; and, examination and disposal of fetal tissue.[104] One legal analysis found that although some of "these laws ... make little sense in the context of medical abortion, ... most abortion restrictions are broadly written and could be interpreted by state officials as applying to medical abortion."[105] These same authors point out that because some state abortion laws impose an undue burden on access when applied to medical abortion, they may be vulnerable to legal challenge. Some state legislatures are considering bills that would limit access to RU-486.[106]

European countries where RU-486 is approved have shown a pattern of gradual increase in use of the drug for early abortion. In France, RU-486 was used in 15% of women undergoing abortions in 1994, 21% in 1996 and 26% in 1998.[107] The drug began being used in Edinburgh, Scotland, in 1991, and by "1994, 57% of women there who were less than 9 weeks pregnant and wanted to terminate the pregnancy requested medical termination."[108] In Sweden, following approval of RU-486 in 1992, educational courses for physicians on medical abortion were arranged around the country by the drug company and the Swedish Society of Obstetrics and Gynecology. Use of the medical method grew fairly slowly "from 7% in 1993 to 32% in 1998 and more than 40% in 1999. Several reasons may explain the slow increase. The most important seems to be physician reluctance to use a treatment associated with more pain and bleeding than vacuum aspiration."[109]

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[103]For additional perspective on the reluctance of doctors to provide medical abortion, see: Joffe, C. Medical abortion and the potential for new abortion providers: a cautionary tale. *Journal of the American Medical Women's Association*, v. 55, supplement 2000. p. 151-154; and, Kolata, G. Doctors looking at abortion pill are often unaware of obstacles. *New York Times*, Sept. 30, 2000.

[104]Borgmann, C.E., and B. Scott Jones. Legal issues in the provision of medical abortion. *American Journal of Obstetrics and Gynecology*, v. 183, Aug. 2000 supplement. p. S84-S94.

[105]Jones, B., and S. Heller. Providing medical abortion: legal issues of relevance to providers. *Journal of the American Medical Women's Association*, v. 55, supplement 2000. p. 145-150.

[106]Claiborne, W. Abortion foes want states to curb RU-486. *Washington Post*, Oct. 5, 2000. p. A1.

[107]Christin-Maitre, Medical termination of pregnancy, p. 954.

[108]Ibid.

[109]Bygdeman, M., et al. Medical termination of early pregnancy: the Swedish experience. *Journal of the American Medical Women's Association*, v. 55, supplement 2000. p. 195-197.

Some believe the driving force that will bring mifepristone to private doctors' offices will be the women who demand it, and many women in the general public do seem to be very interested in the drug. The National Abortion Federation reports receiving 3,000 calls per month, and the calls are increasing in number.[110] Planned Parenthood Association of America indicates it has "been deluged with calls. We're taking tens of thousands of calls here."[111] "Doctors at abortion clinics also say they have been inundated with calls from women who are interested in mifepristone. [However,] most of the women are confused about what the drug does."[112] A common misconception in the lay public (and even some physicians) is that RU-486 is "a nice, easy way to get rid of a pregnancy."[113] Abortion providers inform women that although the drug is an option, "surgery is faster and less painful and requires one visit to the clinic rather than three."[114]

Large scale surveys of women who have taken RU-486 in clinical trials indicate a high level of patient satisfaction with the drug. The Population Council trial which ended in 1995 found that 88% of the 2,121 women thought that RU-486 was "very to moderately satisfactory," and 96% of those surveyed would recommend it to friends or relatives.[115] Even when the method failed, 70% said they would try it again. However, "women who prefer the method would be loathe to call it easy. Medical abortion requires stamina, patience and tolerance for bleeding. ...It can cause nausea and diarrhea, and it always causes cramps. [In contrast to the surgical method, in which] you lie there and it's done."[116] Many women consider medical abortion to be safer than surgical abortion which poses the risks of anesthesia, infection and damage to the uterus and cervix. Medical abortion is less convenient than surgical abortion; expulsion of the fetus can occur any time, any place after the first pills are swallowed.

According to the Population Council, a woman might choose a medical abortion over a surgical abortion because:[117]

- it can be used in the earliest weeks following fertilization;
- it requires no invasive procedure or surgery;
- it requires no anesthesia;
- side effects tend to be moderate;
- it does not have the risk of uterine perforation or injury to the cervix;
- it has the potential for greater privacy; and

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[110]Kolata, Wary doctors spurn new abortion pill, p. F1.

[111]Ibid.

[112]Ibid.

[113]Ibid.

[114]Ibid.

[115]Kaufman, M. For one woman, drug was the right choice. *Washington Post*, Sept. 29, 2000. p. A18.

[116]Talbot, The little white bombshell, p. 61.

[117]Population Council, *Frequently Asked Questions*. [www.popcouncil.org/faqs/abortion.html].

- some women feel they have greater control over their own bodies; when they use the medical abortion procedure.

A woman might choose a surgical abortion over a medical abortion because:

- it requires fewer office visits and is over quickly;
- it is slightly more effective than medical abortion; and
- the woman notices less blood loss and is unaware of the passing of the product of conception.

Other Methods of Medical Abortion

Following the 1989 decision by Roussel to stop providing RU-486 for abortion research in the United States, researchers here began searching for other substances to provide medical abortion. A paper published in 1991 on the use of methotrexate in treating ectopic pregnancies caused researchers to turn to this drug as a possible alternative to RU-486.[118] In 1993, investigators at University of California published a preliminary study combining methotrexate with misoprostal for early abortion.[119] The method received attention in the press and in the medical community in 1994 when Dr. Richard Hausknecht,[120] a gynecologist and long-time abortion rights activist with a private practice in New York City, announced that he had administered this drug combination to 126 women: 121 of the women had a successful abortion, and five required surgery to complete the procedure.[121] He subsequently reported in the medical literature a 96% success rate among 178 women who received methotrexate followed by misoprostol.[122]

Although efficacy is similar to the RU-486 and misoprostol combination, the various methotrexate regimens do not act as quickly and predictably. Methotrexate terminates pregnancy by blocking the action of folic acid and interfering with DNA synthesis so that fetal cells cannot divide. "Because methotrexate has already been approved by FDA for other purposes, U.S. physicians can legally use this medication for the "off label" purpose of abortion induction."[123] It has been used for a long time as a treatment for cancer, psoriasis, rheumatoid arthritis, and more recently to treat

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[118]Stovall, T.G., et al. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstetrics and Gynecology*, v. 77, 1991. p. 754-757.

[119]Creinin, M.D., and Darney, P.D. Methotrexate and misoprostol for early abortion. *Contraception*, v. 48, 1993. p. 339-348.

[120]Dr. Richard U. Hausknecht is currently the medical director for Danco Laboratories.

[121]Tierney, J. A lone doctor adopts drug for abortion. *New York Times*, Oct. 10, 1994. p. A1, B12.

[122]Hausknecht, R.U. Methotrexate and misoprostol to terminate early pregnancy. *New England Journal of Medicine*, v. 333, Aug. 31, 1995. p. 537-540.

[123]Joffe, Medical abortion in social context, p. S11.

ectopic pregnancies.[124] As of April 2000, the National Abortion Federation listed 116 providers of medical abortion who use methotrexate.[125]

Prostaglandins began to be examined in research protocols during the 1970s as a possible medical abortion agent. However, the most effective dosages had unacceptably high rates of side effects, such as nausea, vomiting, diarrhea, fever, chills, dizziness, rashes, and severe abdominal pain. The prostaglandin misoprostol, which was originally approved by FDA for the treatment of gastric ulcers, has also been investigated by itself as an abortion drug. So far in clinical trials, it too has been found to have unacceptably high rates of side effects. Misoprostol is relatively inexpensive, and unlike other prostaglandins, is stable at room temperature. In countries where abortion is illegal, such as Brazil, misoprostol (often referred to as the *star pill* because of its shape) has been used by poor women to initiate the abortion process.[126] The woman would then report to a health clinic as if she were undergoing a spontaneous abortion which required surgical attention.

Misoprostol has a number of other uses at various stages of pregnancy, such as induction of labor and treatment of postpartum hemorrhage.[127] In fact, misoprostol has been used so frequently and effectively that it has become the treatment of choice in the induction of labor, and has been recognized as such by the American College of Obstetricians and Gynecologists.[128] "Misoprostol is one of the most important medications in obstetrical practice, yet its use in pregnant women remains unapproved by the FDA."[129] "Current product labeling includes a warning that misoprostol is contraindicated during pregnancy because of its abortifacient properties. However, FDA recognizes that, in certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice. Prescribing a medication for an off-label indication is common in the treatment of pregnant women and is not considered experimental if based on sound scientific evidence."[130]

On August 23, 2000, Searle, the manufacturer of the prostaglandin misoprostol (trade name Cytotec), sent a letter to physicians reminding them that their drug is contraindicated for use in pregnant women.[131] The letter provoked "a response from many hospital attorneys, administrators, and pharmacies – an automatic refusal to allow misoprostol to be dispensed or used. ...The timing of the letter, just 2 weeks

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[124]Hausknecht, Methotrexate and misoprostol to terminate early pregnancy, p. 537.

[125]Joffe, Medical abortion in social context, p. S11.

[126]Brooke, J. Ulcer drug tied to numerous abortions in Brazil. *New York Times*, May 19, 1993. p. C13.

[127]Goldberg, A.B., et al. Misoprostol and pregnancy. *New England Journal of Medicine*, v. 344, Jan. 4, 2001. p. 38-47.

[128]Hale, R.W., and S. Zinberg. Use of misoprostol in pregnancy. *New England Journal of Medicine*, v. 344, Jan. 4, 2001. p. 59-60.

[129]Goldberg, Misoprostol and pregnancy, p. 45.

[130]Ibid., p. 38.

[131]Searle Cytotec pregnancy reminder issued as RU-486 action nears. *Pink Sheet*, Aug. 28, 2000. p. 14.

before the FDA announced its approval of mifepristone, left many people wondering whether there were other motivations for Searle's actions."[132] The company states that its letter "resulted from lengthy discussions between Searle and FDA after reports were received of uterine rupture in connection with off-label use of Cytotec in pregnant women. ...The fact that [the letter] was distributed just over a month before the FDA approval of mifepristone was entirely coincidental."[133] Searle is currently working with the FDA to revise the labeling of misoprostol.[134] At the present time, Searle, a unit of Monsanto, is the only U.S. manufacturer of misoprostol; Monsanto merged with Pharmacia in 2000.[135]

Other Uses of RU-486

Mifepristone was originally designed by the scientists at Roussel as a antiglucocorticoid. These drugs interfere with certain adrenal gland hormones, such as cortisol, involved in the regulation of tissues throughout the body. It was only inadvertently discovered to have the antiprogesterone effects which make it useful as an abortion agent. Potential applications that take advantage of the drug's antiglucocorticoid effects include the treatment of glaucoma and Cushing's syndrome, a condition in which dangerously high levels of cortisol are produced by the body.

Mifepristone has also been investigated as a post-coital contraceptive, or *morning after pill*. In this case, the drug would be used within a few hours or days of intercourse in order to prevent pregnancy, certainly before a woman even knows if she is pregnant. Currently, there are several highly effective post-coital contraceptives available on the market, including high-dose estrogen and estrogen-progesterone combinations. However, these treatments are effective only before implantation occurs, and therefore are most effective within 72 hours of unprotected intercourse. In contrast, "mifepristone is effective regardless of implantation and can be administered up to 12 to 17 days after intercourse. In repeated studies, a single 600 mg. dose of mifepristone alone has been shown to be 94% to 100% effective for preventing pregnancy when administered almost anytime before the expected date of menses."[136] When compared with other post-coital contraceptives, mifepristone was as effective and produced fewer side effects. Because of these findings, mifepristone is also being investigated as a monthly birth control treatment.

Other potential uses of mifepristone include menstrual regulation and a treatment for fibroid tumors, a condition that can cause pain and heavy bleeding that sometimes leads to a hysterectomy. It is also being investigated as a treatment for endometriosis,

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[132]Hale and Zinberg, Use of misoprostol in pregnancy, p. 59-60.

[133]Friedman, M.A. Manufacturer's warning regarding unapproved uses of misoprostol. *New England Journal of Medicine*, v. 344, Jan. 4, 2001. p. 61.

[134]Pharmacia *Cytotec* use for labor induction reaffirmed by ACOG. *Pink Sheet*, Oct. 16, 2000. p. 23.

[135]Zimmerman, R. Drug maker tries to slip out of RU-486 controversy. *Wall Street Journal*, Oct. 24, 2000. p. D1.

[136]Goldberg, J.R., et al. Mifepristone (RU-486): current knowledge and future prospects. *Archives of Family Medicine*, May/June 1998. p. 219-222.

a condition in which tissue resembling the uterine lining grows in other locations. It is thought to be a leading cause of female infertility. Small clinical trials of the drug have shown that mifepristone can reduce pain in women with endometriosis, but it is unclear whether the amount of tissue outside the uterus actually decreases. The drug that helps some women end unwanted pregnancies may eventually help others have children. Mifepristone has been shown to be effective for labor induction in postdate pregnancies.

Finally, mifepristone has been used to treat meningioma, a type of benign tumor that arises from the tissue covering the brain or spinal cord. When the tumor cannot be surgically removed, treatment with mifepristone has been tried because the tumor's growth is often stimulated by progesterone, and the drug blocks the action of this hormone. For similar reasons, mifepristone is being looked at as a potential treatment for breast cancer and prostate cancer.

Congressional Actions

The 107th Congress will likely consider legislation on RU-486. Prior to the FDA approval, three times (for FY1999, FY2000, FY2001) the House considered attaching an amendment to the agriculture appropriation bill that would "prohibit any funds to be used by the FDA for the testing, development, or approval (including approval of production, manufacturing or distribution) of any drug for the chemical inducement of abortion." The final version of the bill in all three cases, however, did not contain the amendment language. The FDA approved RU-486 for termination of early pregnancy on September 28, 2000.

On February 6, 2001, the RU-486 Patient Health and Safety Act was introduced by Representative David Vitter in the House (H.R. 482) and Senator Tim Hutchinson in the Senate (S. 251). The legislation would reinstate restrictions FDA had listed in its June 2000 letter to the Population Council and Danco. The same bill language was introduced in the second session of the 106th Congress by Representative Tom Coburn (H.R. 5385) and Senator Hutchinson (S. 3157). The bill stipulates that physicians prescribing the drug must meet the following requirements: (1) qualified to handle complications resulting from an incomplete abortion or ectopic pregnancy; (2) trained to perform surgical abortions and met all applicable legal requirements to perform such abortions; (3) certified for ultrasound dating of pregnancy and detecting ectopic pregnancy; (4) completed a program regarding the prescribing of such drug that uses a curriculum approved by the Secretary of HHS; and (5) have admitting privileges at a hospital located 1 hour or less away from the physician's medical office.

In the opinion of the National Abortion Federation, this legislation represents an unprecedented intrusion into the jurisdiction of FDA and the practice of medicine.[137] They point out that FDA reviewed all the scientific data reflecting the experiences of thousands of women and the agency rejected most of these requirements as medically unnecessary.

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[137]S. 251/H.R. 482 would impose restrictions on RU-486 (mifepristone) already rejected as medically unnecessary by the FDA. *National Abortion Federation Fact Sheet*, Feb. 2001.

Apart from issues related to approval or conditions for use by physicians, RU-486 also raises issues related to federal funding for health programs that might provide access to the drug for women seeking an abortion. The Hyde Amendment has attached to annual appropriation bills for many years a prohibition on the use of federal funds for abortion except in the case of rape, incest or if the life of the woman is in danger. Because RU-486 is used in an abortion procedure, its use under these federal health programs would also be prohibited and the same exceptions would apply. Women relying on such programs as Medicaid, Community Health Centers, and clinics funded by Maternal and Child Health Block Grants will not have access to federal support for their use of RU-486.