surgery, both of the pain attending and complications. A women's prior medical or surgical history is important, and even her friend's stories of her experiences affect her decision.

Women with a history of sexual or physical abuse are profoundly affected. It profoundly affects the comfort and trust around gynecologic procedures. And almost all women who chose this option approached it feeling less fearful and that it was more natural.

How women tolerate early pregnancy symptoms is also at issue. Some women are so nauseated at four weeks of pregnancy that waiting two or three more weeks for a surgical option is really a significant burden, and bleeding is infinitely preferable. Even women who are physically well simply prefer not to wait. The bulk of our current calls are from women very early in pregnancy who seek a method available to them at a time when surgery is not.

Providers and patients all felt that this was a method safe enough to be done at home with adequate counseling and a good backup process. I regularly advise my patients who are miscarrying to stay at home unless they are too uncomfortable or bleeding too heavily, in which case they are welcome to come in.

Many women will still prefer the group setting or

a more closely monitored setting, and both options seem reasonable to me. Women liked initiating the procedure themselves, and they appreciated how it involved their natural physiology.

Clinic staff noted that because women were relieved of the angst many have around surgery, they were able to be present, more intellectually and emotionally present to their abortion decision and process.

Of the patients who came to surgical evacuation, only a fraction had ongoing pregnancies, and these were essentially all in the later gestational ages. Only one or two of our suctions were for worrisome bleeding, many less than would be expected in a similar number of obstetrical patients.

Because of the way abortion medicine is practiced in America, again by providers who are very conscientious about bleeding and very comfortable with surgical approach, I know we were quicker to offer suction than were our European providers.

I also know that women across America regularly drive one to two to eight hours to access abortion services. Even 90 percent odds of avoiding a long drive and receiving services in a familiar setting will look good to many.

Mifepristone will not replace surgical abortion.

It is simply the first option to surgery women have ever had the luxury of choosing. A woman's choice will depend on all the issues I have discussed, as well as who she can get to watch the kids and what her work schedule looks like for the upcoming week.

A great topic of conversation among the women tending the women undergoing medical abortion in our clinic was who would choose what route and why, and some certain all along that they would choose one method or the others, and others who vacillated back and forth depending upon the circumstance.

I have two favorite sayings when I teach residents. The simplest, most basic is that women bleed, and the second is that nothing can bleed as much as a pregnant uterus. Whether a pregnant woman chooses birth, abortion, or suffers a miscarriage, her risk of bleeding is higher than if she were not pregnant; the risk of bleeding with pregnancy and birth, at least an order of magnitude higher than with any first trimester loss.

It is a sad sequela of the political conflict around reproductive medicine that women believe birth control and abortion are more dangerous than birth, and it is a testimonial to women's commitment to autonomy in this profoundly personal arena that they seek services despite this misconception.

I am proud to practice medicine at a time when maternal mortality is drastically lower than it has ever been historically, the final plummet directly attributable to the legalization of abortion services in the early 1970s.

This drug will not increase the risk of maternal hemorrhage. Improved access and earlier treatment will lessen it. A woman's bleeding is a simple fact of our reproductive physiology, incredibly well tolerated and, at some level, irreducible.

American medicine stands in first in so many arenas. American women have long suffered by the separation of abortion services from their routine health care setting and by not having access to the state of the art in reproductive medicine.

They drive far from home, have surgery, and drive back. Hardly the best we can do. They want another option, one that has been used safely by hundreds of thousands of women worldwide, one that works in concert with our own bodies.

Abortion is not on trial here. A drug that has among its many uses a safe, effective alternative is.

I am confident that scientific truth and the wishes of American women will be honored here, and I am grateful for your assistance in bringing American women the

improved standard of health care that they deserve. We will all be healthier as a consequence.

[Applause.]

DR. DAVIDSON: Are there any questions?

DR. NARRIGAN: Could I just ask how many clients you're talking about treating during your study?

DR. NEWHALL: We had 176 in Oregon.

DR. NARRIGAN: Thank you.

DR. KESSLER: The four-hour period of observation that I believe is in the labeling, can you comment on that?

DR. NEWHALL: Yeah. The bulk of women in our clinic were completed with their -- had had their abortions completed by the time that they left the clinic. I would say, you know, again guesstimating because I don't have precise numbers, about half.

There were a number of women who had ongoing pregnancies by ultrasound at the time they left that completed it in the next 24 hours, as Dr. Bardin showed.

We, I think, didn't have any ongoing -- you know, I think it is going to be really important to look at the number of women who have ongoing pregnancies as opposed to those who have uterine debris, if you will. I consider a failure those women who have ongoing pregnancies, and we had very few of those, and the ones we did have were in the later gestational ages.

DR. KESSLER: But based on your clinical judgment, is the four hours in the labeling too long, too short, or is it appropriate?

DR. NEWHALL: I think it is variable. I think some women will -- I think there's a lot of women who could absolutely take this drug at home, and I think there's a lot of women who will only feel comfortable with it if they're observed. And I think it will vary.

I think what will happen in the American setting is that women will come in the morning, take the misoprostol, and they'll go home whenever they feel comfortable about it. I think that it will range widely, and I think a lot will have to do with the comfort of the women themselves, both physically and mentally, around the process.

DR. KESSLER: And the physician? When does the physician become comfortable?

DR. NEWHALL: Again, our physicians were really quite okay about it. You know, as I say, I regularly manage women with miscarriages at home, and so I'm really very comfortable with it.

Women vary a lot in what they're comfortable with, but I think a lot of times when you're comfortable, they're comfortable. You know, they just want to know that this is okay. And, really, I am impressed in my experience

how rarely women become profoundly anemic, with all of the bleeding that they do. I mean, they describe huge amounts of bleeding, and you check their creatinine and it's 38. You know, it's astonishing, and I've come to, you know, depend upon that. It's true.

DR. HENDERSON: Dr. Newhall, can you describe for me your patient population? I mean, who are the women who come to see you?

DR. NEWHALL: My private practice name is Every Woman's Health, and we have a very broad selection of women. My practice is in inner-city Portland, such as it is, and I have a broad ethnic variety. I have a broad social-economic variety. We got the award from the OB-GYN department for the most languages spoken in our clinic. I would say it's as broad as you can find in, you know, America.

DR. DAVIDSON: What is your experience with contraception related either before or after these procedures?

DR. NEWHALL: We always discuss contraception with absolutely every woman, and we offer her a method, and on our form for discharge (it) includes the method chosen by the woman, so that we either provide the method or we make sure that she has a follow-up to a clinic that does provide the method. We provide birth control methods in

our clinic and we either, you know, as I say, provide it if she chooses birth control pills, for example; or if she chooses a diaphragm, we'll arrange for her to have an appointment.

DR. DAVIDSON: Any further questions?

DR. NEWHALL: Thank you.

DR. DAVIDSON: If not, are there any other concluding remarks, observations from The Population Council?

DR. NEWHALL: Ann Robbins is going to summarize our presentation.

DR. ROBBINS: Thank you.

This concludes the formal presentations by The Population Council. As I stated at the onset, the data that you've heard today demonstrate the following: number one, mifepristone and misoprostol is an effective method for pregnancy termination. As Dr. Spitz presented, 95.5 percent efficacy rate was shown in the pivotal trials that were conducted in France. This is similar to the published international data, and our preliminary unaudited assessment of the U.S. data indicates the efficacy from our trial will be within a similar range.

Number two. Mifepristone and misoprostol is a safe method for pregnancy termination. As you've heard from Dr. Bardin, there were no unexpected serious adverse

events in the pivotal trials in France, and this is the same for the trials that were conducted in the United States.

Secondly, the vast majority of adverse events are those that are actually required for the method to work and are a consequence of the pharmacological action of the drug.

Thirdly, mifepristone and misoprostol is an acceptable method to U.S. women. As you've heard, the overwhelming majority of users are satisfied with the method, they would use it again or recommend it to a friend, and they prefer it over surgical abortion. They like it because it allows them to avoid surgery, they find it's more natural, and it allows them more autonomy and control.

And finally, this is a method that is feasible to deliver within the U.S. health care system. Although the primary source of the data you saw were conducted in France, the trial that was conducted in the United States used this exact same regime. It was able to be conducted here in a very similar fashion.

We've heard a very positive but yet a very typical description of an abortion clinic, one that was a family planning clinic here. This has been provided in a variety of other types of clinical settings.

While some aspects of the management of medical abortion are going to be different from those of surgical abortion, particularly in the management of bleeding, the learning curve for health care providers is rapid, women tolerate this, and the vast majority of providers support this use and welcome it.

Therefore, we conclude that mifepristone and misoprostol is a safe, effective, and acceptable method of medical abortion that can be delivered in the United States.

We request approval for the use of mifepristone and misoprostol for pregnancy termination in women with pregnancies of 49 days or less.

Thank you for your attention today.

DR. DAVIDSON: Thank you.

Are there any final questions that the committee might have at this point?

[No response.]

If not, thank you very much.

The Reproductive and Urologic Drug Products Division is the reviewing division for this new drug application, and Dr. Rarick will introduce these presentations.

Agenda Item: Presentations by the FDA Reviewing Division

DR. RARICK: First I wanted to thank the Pop Council for letting me first say good morning, I was debating which I was going to be able to say, and I do appreciate your keeping within your time, and I hope we can do as well from the division.

As mentioned, I am Dr. Rarick, the acting director of the Division of Reproductive and Urologic Drug Products, the reviewing division for this application. I thought we might go through just a couple of minutes of how an NDA is reviewed.

As mentioned, this submission was received in March. When it comes to the reviewing division, it is distributed to several types of disciplines that review the application. There is a clinical review, a pharm-tox review, a review of the chemistry and manufacturing control section. A review is set for a statistical analysis and review, and biopharmaceutics does a review of pharmacokinetics in humans.

A filing decision for a new drug application has to be made. Just because something is submitted to us does not mean that we decide we can review it. A filing decision is made within 60 days of a submission, and during those 60 days it is decided what kind of inspections are needed to be completed. In this case chemistry and manufacturing sites were inspected, as well as clinical

sites in France.

The reviews and inspections need to be completed during the review time, and as mentioned previously, the goal for the Center of Drug Evaluation and Research is to act upon priority applications within six months.

So what are we doing here today? How does the advisory committee fit it? We consider the advisory committee part of our review process. That is why we are here before our six-month time slot. We want them to evaluate and consider the safety and effectiveness of this regimen. We consider this an opportunity for expert advice on this application. We also consider it an opportunity for public comment and for the discussion to be in the public arena.

Our FDA presentation this afternoon will first be a review of pharmacology and toxicology by Dr. Alex Jordan, our team leader for pharmacology in the review division. The clinical review will be split between Dr. Ridgely Bennett, the medical officer for this application -- he will review the non-U.S. studies. You will see some of the same information but a slightly different analysis -- and I will be reviewing the U.S. preliminary findings.

Considerations for safe use will also be discussed. I will do that as part of my review.

You will see that biopharmaceutics and the

statistical reviews and chemistry reviews are not up there. In terms of the biopharmaceutics review, the pharmacokineticist's review did not reveal any significant information relevant to the discussion here today about human safety and effectiveness. The statistical review is a descriptive analysis of the findings, and it is incorporated in the clinical review. And, as Dr. Kessler already noted, any outstanding chemistry issues will be addressed directly with the sponsor.

So let's start by hearing from Dr. Jordan.

DR. JORDAN: Thank you, Lisa.

The members of the committee, I would just like to have a brief overview of the pharmacology and toxicology data for mifepristone.

Basically, as everyone knows, the activity of mifepristone specifically is as an antiprogestogen. But it also has strong glucocorticoid antagonism and even some slight androgen antagonist activity.

It has little or no activity as a mineralocorticoid, either agonist or antagonist, and has little or no antagonist or agonist activity as an estrogen and very little, if any, agonist activity as a progesterone.

The sponsors have looked at special pharmacology studies. These are studies specifically looking at

different organ systems and the effect of the drug on these systems.

In general, the effects were very mild. In the nervous system, there was a potentiation of hexobarbital sleeping time in mice. The cardiovascular/respiratory system, there was no effects, although the doses used were somewhat low in that study. No effects were seen in the gastrointestinal studies. In the genitourinary studies, there was a decreased excretion of sodium and potassium in the animals.

Endocrine system, there was only a slight hypoglycemia in fasted animals, and there were no effects in the hematology or analgesic and anti-inflammatory effects. And most of the effects that we did see here were probably due to the antiglucocorticoid effects of mifepristone.

Pharmacokinetics. Basically, mifepristone is well absorbed in both rats and monkeys. Rats and monkeys were the two species used in the toxicology studies, by the way, up to 75 percent.

The bioavailability, however, the systemic circulation levels of the drug, was only 39 percent in rats and even smaller, 15 percent, in monkeys, and this indicates that the drug, although absorbed is probably or is metabolized quite extensively, probably by the liver,

possibly by the intestines. In fact, in the monkey, the bioavailability was so low that the drug blood levels were probably very low in the toxicology studies.

The metabolite profile was very similar between rats, monkeys, and humans. The important aspect of this is that mifepristone is quite extensively metabolized, and some of the metabolites have biological activity, and all those metabolites that were present in the human were also present in rats and monkeys, and this is important because those metabolites then were tested in the toxicology studies in rats and monkeys.

Just go to the toxicology studies. These were single-dose studies in rats, mice, and dogs at a dose of 1,000 milligrams per kilogram. To put this into some perspective, the 600-milligram dose for women for a typical 50-kilogram woman, that would be 12 milligrams per kilogram for most women, small women, anyway.

There was a single death in male rats. There was some, obviously, toxicity in the rodents, usually a hunched back, ambulatory difficulties, distension of the stomach. As far as the dog goes, the toxicities actually were limited mainly just to vomiting and diarrhea.

Longer term studies were also done. In this case there was a one-month rat study with doses up to 200 milligrams per kilogram. There was no mortality. There

were certain changes in clinical chemistry parameters, some, as you can see, fatty degeneration of liver only in the high-dose females, and almost all the changes or the toxicities attributable to the drug were due to the antiglucocorticoid and/or the antiprogestogen effects of mifepristone.

In the monkey, this was a one-month monkey study in cynomolgus monkeys. The high dose here was 100 milligrams per kilogram. And as you can see, the monkeys are much more sensitive to this drug than are rats. In fact in the high dose, two high-dose and one mid-dose monkey were sacrificed moribund or very sick. They had suffered from reduced appetite, body weight loss, vomiting, and diarrhea. Again, I think many of these effects were due to the antiglucocorticoid properties of the drug. There was no real histopathology in these monkeys.

The company also did two studies, two six-month studies in rats -- well, a six-month study in rats and a six-month study in monkeys. The six-month study in monkeys utilized a high dose of 45 milligrams per kilogram, and there were no deaths in that study.

Getting on to the reproductive toxicology studies, in the return-to-fertility studies that were conducted in rats, there were two doses, up to 3 milligrams per kilogram used, and the estrous cycle in these rats was

disrupted during the 21-day treatment. Actually, it was disrupted probably within the first 10 days.

Drug was withdrawn, and then, over the next five weeks, the animals gradually resumed cycling estrous cycles. They were then mated to normal males, and gestation, parturition, litter size, the morphology of the offspring, body weight, and survival were not affected by this treatment. So, basically, mifepristone doesn't seem to have any effect on fertility.

Getting into the effects of mifepristone directly on the embryo or fetus, the company did studies in mice, rats, and rabbits. The protocol for these studies, the drug was given from time of implantation, which is around day 6 of pregnancy, until late in pregnancy, not too late, in day 17 -- it was given until day 17 in rats and mice; day 18 in rabbits. There were no teratogenic effects in mice or rat.

In rabbits it wasn't quite as clear cut. I can just lead you through this slide, if I may. The number of fetuses examined, you can see the top, the doses were zero, .25, .5, and 1 milligram per kilogram. I am focusing now on malformations of basically the head, then cranium, because these were the most prevalent.

Acephaly or sort of lack of head development occurred in one sort of mid-dose animal. Exencephaly,

where you had a failure of the cranium to close, essentially, happened in a control animal; that is, an animal that did not receive the drug at all. And then another exencephaly also occurred in a low-dose animal.

The company then went ahead and did a supplemental rabbit study with higher doses. In this case the doses went up to 4 milligrams per kilogram, and as you can see, since there was the same number, there were, I think, 20 rabbits per group here; in the 4-milligram-per-kilogram there were only 54 fetuses, indicating there were many abortions in this dose group. In fact, there were many abortions, or a few abortions, also, in the 2-milligram-per-kilogram.

Nevertheless, there was another exencephaly and other malformations in one mid-dose and a cleft palate in another mid-dose without any malformations in any of the controls. These data alone, which were submitted by the sponsor in the NDA, for us reviewers this would not really raise too much of an alarm because you have no dose response here; you have effects in the controls.

However, there was a published report by Jost in 1986 using a different strain of rabbit, 10 per group, with the doses seen there. Now, those doses are actually fairly low; they only go up to 1 milligram per rabbit, which is approximately .33 milligrams per kilogram.

There were 10 per group, so there were 40 rabbits. Twenty-two of them had abortions. Eighteen had normal or partial pregnancies. In those 18, three rabbits in the .75-milligram-per-kilogram dose group had similar malformations as was shown in the previous studies, and one rabbit in the high-dose group also had these malformations, exencephaly, acephaly, those types of malformations.

So the data together from all three studies indicate that there is highly -- well, I wouldn't say highly, but a probability that mifepristone is teratogenic in rabbits.

They also did a battery of genetic toxicology studies looking at the ability of mifepristone to cause mutations or chromosomal aberrations. These studies, seven total, six of them in vitro studies and the last one, the micronucleus test in vivo, were uniformly negative. So there doesn't seem to be any ability of mifepristone to cause any genetic or DNA damage.

So, basically, my conclusion is in the pharmacology that mifepristone does give the expected antiprogestin/antiglucocorticoid effects. The general toxicology, there is no unexpected toxicity. The reproductive toxicology, there is no effect on return of fertility. There is a possible teratogenic effect in rabbits, and it is negative in seven tests.

My conclusion is that mifepristone has been adequately tested in a wide variety of pharmacologic and toxicologic studies. The results demonstrate that mifepristone has the expected pharmacologic activity and no unusual or unexpected toxicity -- has the expected pharmacological activity and no unusual or unexpected toxicity.

The non-clinical testing program more than satisfies the regulatory requirements for a drug to be administered as a single dose.

Thank you.

DR. DAVIDSON: Are there any questions from the committee? Yes, Dr. Petitti?

DR. PETITTI: Did you review studies of the embryotoxicity of misoprostol as part of your review?

DR. JORDAN: Yes, I did. I might have a slide.

Well, basically, if you look at just the PDR for misopristol, embryotoxicity is negative. It says in the labeling that there are no teratogenic effects of the drug.

However, we do know that prostaglandin E-1 from other studies has had teratogenic effects in rats. So there is that; also, the possibility misoprostol also has some adverse effects on fetuses.

And, also, obviously, there are effects on fertility and decreasing number of live pups and stuff like

that, pretty much the expected pharmacology of that drug.

DR. DAVIDSON: Are there any other questions?

[No response.]

Thank you very much.

The next presentation by Dr. Bennett, review of non-U.S. clinical findings.

DR. BENNETT: Good afternoon.

I would like to review the clinical findings from the pivotal studies of mifepristone and misoprostol to support an indication for the medical termination of intrauterine pregnancy through 49 days' gestational age.

The proposed dosage recommended is three 200-milligram tablets of mifepristone taken in a single oral dose. Unless abortion has occurred and is confirmed by clinical examination or ultrasonographic scan, the patient must also take two 200-microgram tablets of misoprostol two days after ingesting mifepristone. She must remain under medical monitoring and supervision for a period of four hours after administration of the misoprostol.

The efficacy and safety of mifepristone and misoprostol were evaluated in two historically controlled, open-label, multicenter clinical trials in France, which I will designate as studies 14 and 24. Twelve hundred eighty-six subjects were enrolled in study 14 and 1,194 subjects were enrolled in study 24.

Subjects with pregnancies through 49 days' gestational age were included in study 14 and through 63 days' gestational age in study 24.

Subjects in both studies received 600 milligrams of mifepristone followed in two days by misoprostol, 400 micrograms, if abortion had not already occurred.

Subjects in study 24 received one additional dose of 200 micrograms of misoprostol three hours after the first dose if abortion had not occurred.

Women studied were generally 18 to 35 years of age, and a final assessment of the pregnancy termination procedure occurred 8 to 18 days after the administration of mifepristone.

Women were excluded from the study if they smoked 10 or more cigarettes per day, had cardiovascular disease, asthma, glaucoma, or high intraocular pressure, diabetes, hyperlipidemia, or a history of renal, adrenal, or hepatic insufficiency. Also, women were excluded if they had been treated with corticosteroids during the previous six months, were anemic, had a hemostatic abnormality, were using anticoagulants, or lived far away from the clinic.

The outcome of treatment was classified as successful if complete expulsion of the products of conception occurred without the need for surgical intervention. The outcome was classified as failure if

incomplete expulsion of products of conception occurred, if pregnancy continued, or if a surgical procedure was required for hemostatic purposes.

All patients were included in the safety analyses, but some were not included in the sponsor's efficacy analysis because neither an ultrasound nor a beta subunit HCG pregnancy test was performed to confirm pregnancy. Ninety two point five to 93.7 percent of patients enrolled were evaluated for efficacy. Eighty-one subjects in study 14 and 90 subjects in study 24 were excluded from the efficacy analyses for this reason.

Unless otherwise noted, the following results discussed will be based on this efficacy evaluable population. In study 14, where the gestational age was up to 49 days and where the administration of mifepristone was followed by no more than one dose of misoprostol, complete abortion occurred in 95.4 percent of patients. Incomplete expulsion occurred in 2.8 percent of subjects, and the pregnancy continued in 1.5 percent of subjects.

Surgery to stop bleeding was performed in 0.3 percent of subjects.

A few subjects had pregnancies greater than 49 days' gestational age, in violation of the protocol. In those women with longer gestational times, the success rate generally declined with increasing gestational age,

yielding a statistically significant inverse relationship as shown on this slide.

Subjects with pregnancies through 63 days' gestational age were included in study 24. If we look only at subjects with pregnancies up to 49 days' gestational age, we see that the regimen was 95.7 percent successful. We see also that the success rate generally declined with increasing gestational age, as was seen in study 14. This inverse relationship between gestational age and success rate was also statistically significant.

However, in contrast to study 14, the protocol for study 24 provided for one additional tablet of 200 micrograms of misoprostol to be given if complete expulsion had not occurred during the first three hours of the four-hour observation period.

Consequently, the treatment regimen for subjects who received the additional 200 micrograms of misoprostol in study 24 differed from that of study 14, where the subject received only one dose of 400 micrograms of misoprostol.

We were interested in comparing the success rate between similar patient populations in the two studies. Therefore, in this analysis, we focused only on subjects in study 24 whose gestational age did not exceed 49 days and who took no more than one dose of 400 micrograms of

misoprostol. We found that 210 subjects satisfied these criteria.

Two hundred eight of these subjects experienced a complete expulsion for a 99 percent success rate, which was similar to the corresponding 95.4 percent success rate found in study 14.

The sponsor excluded from the efficacy analyses subjects whose pregnancies had not been confirmed either by a sonogram or beta subunit HCG. The sponsor excluded 27 subjects whose outcome was known from its efficacy analysis of study 14 and 20 subjects whose outcome was known from its efficacy analysis of study 24 whose gestational ages did not exceed 49 days and who took no more than one dose of 400 micrograms of misoprostol.

If we include these subjects in our efficacy analysis, the success rates remain unchanged in both studies. That is the 95.4 percent in study 14 and the 99 percent change to 98.7 percent in study 24.

The sponsor also appropriately excluded subjects from the efficacy analysis because the outcome was unknown and pregnancy had not been confirmed by sonography or testing for the beta subunit of HCG. Forty-eight subjects from study 14 were excluded from the efficacy analysis for that reason, as were nine subjects from study 24.

If we were to classify as failures all of these

subjects with an unknown outcome whose gestational age did not exceed 49 days and who took no more than one dose of 400 micrograms of misoprostol, a worst-case analysis yields a success rate of 91.8 percent in study 14 and 95 percent in study 24. The data from these two pivotal studies provide support for the effectiveness of mifepristone plus misoprostol for the medical termination of intrauterine pregnancy through 49 days' gestational age.

To recap, a total of 2,480 subjects were enrolled in the two pivotal studies. The overall success rate was 95.4 percent in study 14, where gestational age did not exceed 49 days and the subjects received no more than one dose of misoprostol; and 92.8 percent in study 24, where gestational age did not exceed 63 days and the subjects received one additional dose of misoprostol if complete expulsion had not occurred during the first three hours of a four-hour observation period.

Adverse events, regardless of the causality assessment, were reported. The incidence rate of adverse events was higher for each event reported in study 24 than in study 14. It is very tempting to speculate that this higher incidence seen in study 24 might be due to the second dose of misoprostol given in that study.

It is not surprising that by far the most commonly reported adverse reaction was painful contractions

of the uterus and/or cramps similar to labor or menstrual cramps. In study 24, these occurred in 86 percent of women, some of whom were treated with analgesics. About 35 percent of women who had this complaint judged the pain to be severe.

Ninety-five percent of all complaints were reported during the three to four hours following administration of misoprostol. Fifty percent of women reported nausea, 29 percent reported vomiting, and over 15 percent of women reported diarrhea.

The only cardiovascular adverse events reported in study 14 were three cases of tachycardia, one judged by the investigator and sponsor to be related to mifepristone, one judged by them to be related to misoprostol, and one judged by them to be unrelated to either drug.

The cardiovascular adverse events reported in study 24 were seven cases of hypotension, three cases of palpitations, two cases of tachycardia, two cases of syncope, and one case of thoracic pain. All of these adverse events were of mild or moderate severity except for one case of hypotension.

Hypertension, defined as systolic pressure greater than 140 millimeters of mercury and/or diastolic pressure greater than 90 millimeters of mercury, was reported during the four-hour observation period following

misoprostol administration in 2.6 percent of patients in study 14 and 2.5 percent of patients in study 24. At the end of the four-hour observation period, the hypertension had resolved spontaneously in most cases.

During the four-hour observation period, 17 percent of patients had a decrease of more than 20 percent from base line in either their systolic or diastolic blood pressure.

Turning now to serious adverse events, we found no patients who were discontinued from studies because of an adverse event, and there were no deaths.

Fifty-two subjects experienced heavy bleeding. To control uterine bleeding, 6 percent of patients in study 14 and 19 percent of patients in study 24 received oxytocin or methyl ergometrine. Five patients in study 14 and 10 patients in study 24 had uterine evacuation procedures performed to control bleeding.

One patient in study 14 and three patients in study 24, one of whom had an ectopic pregnancy, received blood transfusions.

The median duration of uterine bleeding in both studies was eight days. One woman in study 24 reported 69 days of bleeding, and it was noted that bleeding occasionally lasts for 45 days or longer.

Two point three percent of patients in study 14

and 5.4 percent of patients in study 24 had hemoglobin values that declined by more than 20 percent from their pre-mifepristone administration levels. Thirteen point three percent of patients had a decrease in their hemoglobin of at least 2 grams per deciliter. The maximum decrease in any patient was 6.4 grams per deciliter.

Treatment for anemia obviously may be required. One patient's follow-up hemoglobin 6 to 12 days after transfusion was 5.5 grams per deciliter.

Bleeding is an expected consequence of the action of mifepristone as used in this treatment regimen. Withdrawal of the influence of progesterone in the uterus due to its competitive inhibition by mifepristone at the receptor site results in bleeding, disruption of placental function, and disruption of the inhibitory effects of progesterone on the myometrial-stimulating action of prostaglandins.

Mifepristone for the termination of pregnancy has been used in China since 1988, in France since 1989, in the United Kingdom since 1991, and in Sweden since 1992. Over 150,000 women have been treated using the specific dosage regimen of 600 milligrams of mifepristone and 400 micrograms of misoprostol.

The experience to date in France, the United Kingdom, and Sweden has been under controlled conditions

with mifepristone available to patients only in registered or approved facilities.

Surgical abortion utilizing the vacuum aspiration-suction-curettage method for the termination of pregnancy has been in widespread use for over 25 years. During this time its safety has been extensively studied and the rates of complications of the procedure reported to increase with increasing gestational age.

The failure rate of the procedure -- that is, the inability to terminate the pregnancy effectively -- increases with decreasing gestational age. For this latter reason, many abortion clinics have elected not to perform surgical abortion procedures before six weeks' gestational age, even though pregnancy can be reliably diagnosed prior to the expected day of the menstrual period.

There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.

Thank you.

DR. DAVIDSON: Thank you, Dr. Bennett.

Are there any questions from the committee?

You again noted that the protocol excluded patients with smoking or alcohol consumption. Neither of these are mentioned in the labeling or the patient information leaflet. What implications do these two habits have for clinical use of this drug?

DR. BENNETT: Unless it is specifically listed in the labeling as a contraindication or as a warning, then it could be used in all patients.

DR. DAVIDSON: What was the rationale for excluding these conditions in the protocol?

DR. BENNETT: There was no rationale actually given in the protocol per se for excluding the patients. But I think the presumption was that after the myocardial infarction and one patient who died from one, that one would try to limit patients who might be at higher risk for myocardial infarction.

DR. DAVIDSON: Dr. Henderson?

DR. HENDERSON: A general question. Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?

DR. BENNETT: Well, I think it would be difficult

really to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy. I think one has a pretty good handle on --

DR. HENDERSON: The rate of synchronous --

DR. BENNETT: Yes.

DR. DAVIDSON: Dr. Daling?

DR. DALING: Is there any information on repeated procedures and the length of time between repeated procedures by any one woman?

DR. BENNETT: I know of none.

DR. DAVIDSON: Are there any further questions?

DR. LEWIS: My question is similar to Dr. Daling. You mentioned that certainly surgical abortion is more difficult to do in this early gestational group and that the failure rate is higher. Could you give us some ballpark of what that would be? Obviously, it is not a true control.

DR. BENNETT: Actually, the failure rates for both procedures are fairly comparable for this stage of gestation.

DR. LEWIS: Yes.

DR. DAVIDSON: Are there any further questions?

[No response.]

If not, thank you very much.

DR. RARICK: Again, we will be summarizing the

preliminary safety data from the U.S. clinical studies and reminding the committee of the proposed considerations for use.

These are preliminary safety findings. These are based on reporting to the sponsor. These have not been completely analyzed, and we do not have a final report. We have only the serious adverse event reports to review today.

As you have already heard, there were 52 serious adverse events, there were no deaths, and these types of adverse events were consistent with the foreign trials.

To look at them a little bit more closely, the numbers here you have already seen. There were 16 patients that were hospitalized in these adverse events, and again, I remind the audience that these are reported regardless of the determined causality.

In the number of hospitalized patients, you will see that 20 were hospitalized for what I have reclassified as heavy bleeding, but I will wait for their further analysis for how they decide to call it hemorrhage or menorrhagia or metrorrhagia or all the various words that can be used for this definition.

All of those patients who were hospitalized with bleeding did have suction curettages. Two of these patients had blood transfusions.

The other hospitalizations are listed, one patient each: gunshot; pneumonia; a psychiatric disorder which included anxiety, depression, and a suicide attempt; viral meningitis; and what I am calling from the preliminary review of the data a questionable pelvic inflammatory disease process a patient was hospitalized for.

There were then 26 that were not hospitalized. Again, heavy bleeding was the majority of these cases. In these patients, about half of these patients who were not hospitalized did have a suction curettage, and again, two of these patients underwent blood transfusion.

Three of the patients that were not hospitalized were considered to have serious events as sequelae of nausea, vomiting, and diarrhea. I put them together. The reports include nausea/vomiting dizziness, nausea and vomiting dehydration, diarrhea dehydration, and I lumped those together for today.

There was one vasovagal reaction that was considered a serious adverse event and one case of abdominal pain,

As Dr. Bardin has already shown you, this next slide compares the serious adverse events reported for the U.S. study versus the French studies, the same ones you have already seen.

Special conditions for use. The committee has for their review draft labeling that has been proposed by the sponsor, but I wanted to point out again the issues that we consider from the division to be somewhat unusual although not completely unique to this product. There are other systems with similar things, but it is unusual.

These are in three areas: the delivery system proposed, the provider requirements necessary, and what I am calling patient attributes that are required for this proposal.

In terms of delivery system, we have already heard that it is going to be distributed directly to providers and not to pharmacies, that records would be kept for each dose, and that administration would be given under supervision.

In terms of provider requirements, the current labeling and the current proposal of it is for physicians only for distribution. These are providers that must be trained in dating of pregnancy, the diagnosis of ectopic pregnancy, and how to do a surgical abortion, and they must have access to all these facilities for surgical abortion and emergency treatment.

What I am calling patient attributes, and I am not going to run through the whole labeling of contraindications, warnings, et cetera, but some of the

specific ones for consideration. Obviously, within 49 days of last menstrual period. Also noted that ultrasound can be used as needed to confirm length of gestation. Living requires residing and working within one hour of appropriate medical facilities. They be able to comply with a multiple-visit regime and, of course, comply with the four-hour wait that is currently listed in the draft labeling.

They must also have a written and signed informed consent or decision document. As the committee will probably suggest, we need to work with the sponsor regarding need for multiple language issues and consideration for the illiterate population.

Patients must understand the potential side effects when they sign this informed decision document, and they are also signing the information that they know they may need a surgical intervention.

Dr. Kessler has already reviewed for you the questions that you are going to be asked today at the end of the day. As you can see, number 1 deals with the effectiveness of the regimen. Number 2 relates to the safety of the regimen. Number 3 is an overall risk-benefit question.

Number 4 asks you to consider the labeling for the physician, whether it is too restrictive, whether it is

not restrictive enough. Question number 5 asks you to consider the labeling to the consumers.

Question number 6 asks you to consider the draft proposal for distribution. And question number 7 asks you to consider postmarketing issues and if there are issues that you feel have not been adequately addressed that would need to be addressed postmarketing.

All of those last questions, 4 to 7, are all based on the concept that if the regimen were to be approved in this country, what does the committee consider?

I would like to conclude my remarks by again thanking you, the committee, for your careful consideration. I would like to thank in advance those who will be speaking during the open public session. We look forward to your comments and your voice.

Finally, we look forward to the committee's discussion and recommendations concerning the safety and effectiveness of mifepristone and misoprostol for this indication. Thank you.

Any questions?

DR. DAVIDSON: Dr. Petitti, then Dr. Kessler.

DR. PETITTI: A few weeks ago we saw adverse event reports on emergency contraception from the British Committee on Safety of Medicines. Has that information been reviewed for this --

DR. RARICK: From the United Kingdom and from other countries?

DR. PETITTI: Right, yes.

DR. RARICK: I don't know if Ridgely has this information on him, but we did discover there was postmarketing surveillance information submitted to the IND, I think, in November of 1995 from the United Kingdom. I don't know if they brought it with them; I don't know if we did, either.

DR. PETITTI: Was there anything different from what we've gotten in terms of the overall adverse effects from these trials?

DR. RARICK: As far as I know from that data, we didn't find anything unusual that wouldn't be similar to what has been found in the foreign and U.S. studies.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: I will go, please, after you.

DR. DAVIDSON: Dr. Narrigan?

DR. NARRIGAN: This is just a point of clarification that I need. Again, I am looking at the 2,200-and-some women that you're telling us about and recalling that only 800 of them are in the gestational age of 49 days or less. Am I correct on that?

DR. RARICK: We don't have the data, but they're nodding yes. All we have is their data on the safety

information with serious adverse events.

DR. NARRIGAN: But that's for women who are up to 63 days.

DR. RARICK: Yes.

DR. NARRIGAN: So we really --

DR. RARICK: Because we are looking at the U.S. information to give us a safety profile.

DR. NARRIGAN: But is not the request by the sponsor for only up to 49 days?

DR. RARICK: Correct.

DR. NARRIGAN: Why are we then considering the extra days in these numbers? These are important numbers.

DR. RARICK: Yes, they are very important numbers.

DR. NARRIGAN: What is the difference?

DR. RARICK: You will notice that the French second study also went to 63 days, and we are looking at the whole safety profile of women that are using this regimen for abortion; what kinds of adverse events have we seen? You are absolutely right; if they would like to present the information on only up to 49, if they have that serious adverse event numbers, unless this is only about up to 49 days. No, this is everybody here.

When we look at safety, we like to evaluate everybody who has taken the product even if it is --

DR. NARRIGAN: I see.

DR. RARICK: Even as you heard, there was data presented with sulprostone. When you look at safety, we like you to look at the big picture.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: We just wanted to make sure you had a complete safety database as of this time certainly for serious adverse reactions. That is what we insisted upon.

DR. NARRIGAN: But it may overestimate -- I mean, if half of the people that were hospitalized fell into the group 49 to 63 days, then that is an overestimation.

DR. KESSLER: Your point is well taken.

Can I just ask Dr. Rarick one question? There was one case that did get reported, I believe, in the Iowa press, and there were some questions about whether that case was appropriately reported to the FDA. Is there anything you can tell us about that case?

DR. RARICK: Yes. That was a case that was definitely reported to us by all our standard procedures of a three-day report, a written report, and follow-up reports. We received that case of a patient who was hospitalized, had a D&C and a transfusion, and she is included in this analysis.

DR. DAVIDSON: Dr. Rarick, I am familiar in general with some congruency between the clinical protocol

and the labeling. Would you comment on the question I have raised about alcohol and smoking?

DR. RARICK: Again, I think the protocol inclusion criteria called for leaving those out because of this concept of is this a cardiovascular event risk issue, and until the information could be gathered back to say that maybe with misoprostol it is not as much of an issue, I think those were appropriate inclusion criteria.

In terms of the labeling and whether it is going to record you shouldn't smoke more than -- I think the inclusion criteria was less than 10 cigarettes a day -- if that is something that you feel is still an issue, you need to raise that during your deliberations.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: There was one case of chest pain, just because trying to separate the cardiovascular risk -- is there any more information whether that was cardiac in origin, do you remember?

DR. RARICK: I don't remember. If the sponsor remembers for me -- and I don't have the actual Medwatch forms here today, but I can look into that.

DR. KESSLER: It just may be helpful in trying to sort out Dr. Davidson's concern about smoking.

DR. RARICK: Certainly.

DR. DAVIDSON: It wasn't so much a concern as

just a technical question about the congruency.

DR. RARICK: I would point out that that chest pain case was not also associated with any kind of tachycardia, hypertension or hypotension, or any other cardiovascular-type adverse events. The only code on that form just was chest pain.

DR. DAVIDSON: Okay. Dr. Zoles?

DR. ZONES: I don't recall alcohol being mentioned, any exclusion criteria.

DR. RARICK: I don't think that it was, but I heard somebody say that earlier, and I don't want to disagree with them without noting it myself. I am hearing that it was not an exclusion. I know it wasn't --

PARTICIPANT: Liver disease. Hepatic, liver disease.

DR. RARICK: Right. I heard them say that. I don't we said that, that if they want to confirm whether alcohol was or wasn't an exclusion criteria --

DR. DAVIDSON: Any further questions? Yes, Dr. Azziz?

DR. AZZIZ: Just a question about age. Most of these studies have obviously included patients under the age of 35. There is no -- is that an issue that has been raised and simply we don't think that age is a major issue or --

PARTICIPANT: How do we know?

PARTICIPANT: We don't have data.

DR. AZZIZ: Do we know that if somebody was 42 and takes this drug, is that an issue?

DR. RARICK: I think the French data can be looked at over ages, and I think they have done that. We don't have that information yet for the United States, and I think that is something that if you feel is an issue to be raised during the discussion, you should let us know your thoughts on that.

DR. DAVIDSON: Any further questions?

[No response.]

If not, we will recess for lunch until promptly at 2 o'clock.

[Whereupon, at 12:50 p.m., a recess was taken until 2:00 p.m. the same day.]

AFTERNOON SESSION (2:00 p.m.)

Agenda Item: Open Public Hearing

DR. DAVIDSON: Would the committee reconvene?

[Pause.]

We are now prepared to begin the open public hearing, and as is customary the speakers will please come to the podium here in front. We ask that each speaker give their name, their organization they represent, if any, and any financial interest they may have in the meeting involving payment of travel or other expenses in disclosing any possible conflict of interest, including travel.

We are requesting, due to the length of the presentation list, that each presentation is no longer than four minutes. The timer is on the podium in that regard with three minutes, green; one minute yellow; and then red. It would be most appreciated if you confined yourself to those times.

The list will be announced by Dr. Corfman who will also keep the time. I do not know what his penalties are for not conforming.

[Laughter.]

DR. CORFMAN: Well, we have 34 speakers who are on the list. We do not know if all the speakers have arrived so we will just go down the list as printed in the agenda and if you know of anyone who comes in after their

name has been called please let me know because we want to get everyone -- so everyone has a chance to speak.

We would like you to keep to the four minutes but on the other hand we really want to hear what you have to say. In my view this is really one of the most important parts of the meeting.

The first speaker would be Michael Schwartz, who is speaking on behalf of Congressman Tom Coburn of the U.S. House of Representatives.

Office of Congressman Tom Coburn, Member, U.S. House of Representatives, Michael Schwartz

MR. SCHWARTZ: Thank you very much. "Mr. Chairman, committee members, I oppose licensing RU 486 prostaglandin for abortion because it takes the life of an innocent unborn baby and can injure and possibly even kill women.

"Speaking to you as a practicing obstetrician and Member of Congress I am concerned that the health and possibly even the lives of tens of thousands of American women will be jeopardized because the RU 486 prostaglandin abortion technique is being rushed onto the market without sufficient testing of an objective scientific and medical evaluation by the FDA.

"The citizen petition filed in February 1995 by 23 members of Congress raised many extremely important and

valid issues that must be addressed prior to approval. I would like just to highlight here two particularly troubling ones."

The first point I understand has been -- there has been a change in the proposal so that this drug is proposed for licensing not through the ninth week but through the seventh week of pregnancy, that was a concern that Dr. Coburn addressed in his statement. I will simply touch on the highlights there.

He pointed out that efficacy of the drug drops of sharply after 7 weeks, that the reported complete abortion week up to 49 days is 97.5 percent but the tests show that the rate drops to 89.1 percent in women 50 to 56 days pregnant and 84.4 percent in women 57 to 63 days pregnant. So, while this change has been made since Dr. Coburn drafted this testimony I am sure I want to convey to you his gratitude and support for that change in proposal.

"Second, as discussed in the citizen petition, an acceptable level of safety for RU 486 is contingent on strict patient compliance, including the follow-up visits. For example, failure to return to the abortion facility significantly increases the risks that surgical intervention will be required or other complications will arise and if the prostaglandin is not taken precisely on time the abortion techniques effectiveness declines placing

the woman in jeopardy of having to have surgery." This is citizen petition pages 23 to 27.

"Another hazardous situation occurs with ectopic pregnancy. RU 486 could induce bleeding and give a woman with ectopic pregnancy the erroneous impression that she was no longer pregnant. If the woman fails to return to the abortion facility to verify that she is no longer pregnant the ectopic pregnancy would continue to grow and possibly endanger her life when it ruptures the fallopian tube.

"The lack of an effective means to ensure an adequate level of patient compliance is a serious draw back and, as the citizen petition noted, 'Even under the carefully controlled conditions of a clinical trial patient non-compliance has been a problem.' For example, in a trial in the United Kingdom published in 1990, 9 women were lost to follow-up before the abortionists could confirm that the abortion was complete, 9.35 percent of the women in the study failed to return for follow-up after administration of the prostaglandin and 21.77 percent did not return 9 days after receiving RU 486 and prostaglandin.

"More over, in the U.S. there is no reason to expect that the prospects for patient compliance would be any better than overseas. For example, Dr. Suzanne Pupema, owner of a Seattle abortion facility, participated in the

RU 486 prostaglandin trials, she explained in the April 12, 1993 American Medical News that even though U.S. abortion facilities routinely include follow-up visits in the price of an abortion, 'We're lucky if 30 to 40 percent of these patients ever return.'

"My question is given the current lack of follow-up by U.S. surgical abortion providers and the problems that many non-english speaking, uneducated women would have understanding the instructions how will the FDA ensure that women will comply with the complicated 3 visit RU 486 procedure?

"If I had more time I could address the hazards that RU 486 poses to women with common pre-existing medical conditions, the dangers to unborn children from exposure to RU 486 and prostaglandin and the lack of studies on the impact of women's future facility of taking these 2 powerful synthetic hormones.

"Please keep me informed of the status of the FDA's review of these issues. Thank you."

DR. DAVIDSON: Thank you very much.

DR. CORFMAN: The next speaker is Lisa Kaeser for the Alan Guttmacher Institute.

Alan Guttmacher Institute - Lisa Kaeser, J.D.

MS. KAESER: Good afternoon. I am Lisa Kaeser, representing the Alan Guttmacher Institute, an independent,

non-profit corporation for research, policy analysis, and public education on issues relating to reproductive health. To my knowledge we have no conflict of interest with today's meeting.

We appreciate the opportunity to make a statement regarding the committee's use of mifepristone for the termination of early pregnancy.

As you know, 6 in 10 pregnancies in the United States are unintended, nearly half of these end in abortion. Currently abortion is a legal procedure used by almost half of all women in this country at some point in their lives. Any new method of abortion, including medical abortions such as mifepristone, should be judged and made available based on the scientific evidence of the safety and effectiveness according to the criteria and processes applicable to other medical treatments.

Thus, if the Food and Drug Administrations determines, based on the evidence presented and its own best judgement that mifepristone is safe and effective, it should be approved and a new option can be made available to women in the U.S.

Once the decision to have an abortion is made time is of the essence. The risk of complications, as you know, increases with the length of gestation and most women who have made the decision to terminate pregnancy want to

do so as soon as possible.

Even though currently available surgical methods of abortion are very safe medical methods of abortion could be extremely useful to women who prefer not to have surgery. Moreover, while 98 percent of abortion facilities will provide services at 8 weeks gestation most providers or surgical abortions set minimum gestation limits before which they will not perform the procedure.

According to AGI's most recent abortion providers survey, conducted in 1993, the most common gestational requirement is 6 weeks since a woman's last menstrual period, the criterion used by 43 percent of non-hospital facilities. In fact, only 26 percent of surgical abortion providers offer care to women at 4 or 5 weeks LMP. Some 24 percent of facilities do not provide surgical abortion until women are at least 7 or 8 weeks from LMP, that is at least 5 weeks since conception.

Many of these limitations continue to exist despite the fact that the newest pregnancy tests are highly sensitive, some accurately predicting pregnancy as soon as 10 days after conception and allowing women who ultimately choose abortion to make their decisions earlier. For those who do not want to wait until later in the pregnancy to obtain surgical abortion a medical method that can be used earlier could be highly beneficial.

While the availability of medical abortion has the potential to reduce some of the barriers to abortion services in this country at this time we do not know what kind of eventual impact the approval of mifepristone will have. It would be unrealistic to expect this new method to solve all problems of access. As it is, few providers are available to perform surgical abortions, particularly in some areas of the country.

One of the barriers to health care in the U.S. is insurance coverage. Currently 66 percent of private fee for service and 77 percent of HMOs in the U.S. cover surgical abortion. If mifepristone is deemed by the FDA to be safe and effective for the termination of pregnancy and is approved coverage for this new option should be at least the same as that for surgical abortion.

In addition, the political pressures brought to bear against surgical abortion and its providers have clearly affected the development of medical abortion. Unfortunately, these pressures have also served to slow research on mifepristone and related drugs for other purposes, including their possible uses for contraception.

Should the FDA approve mifepristone we hope these other avenues can be pursued as well. Thank you.

DR. CORFMAN: The next speaker will be Dr. Carolyn Westoff with the American College of

Obstetricians and Gynecologists.

American College of Obstetricians and Gynecologists - Carolyn L. Westoff, M.D.

DR. WESTOFF: Good afternoon. I am Carolyn Westoff. I am an associate professor of OB-GYN and public health at Columbia University. I am also Medical Director of Columbia Presbyterian's Family Planning Clinics and I also served as one of the investigators in the Population Council's trials of mifepristone.

Today I am here to represent the American College of Obstetrics and Gynecology which is an organization of more than 37,000 physicians who are dedicated to improving women's health. We support the approval by the FDA of mifepristone and misoprostol as a non-surgical method for termination of pregnancy up to 49 days from the woman's LMP.

Let me convey ACOG's appreciation to the Population Council for its efforts in conducting the United State's trials and for submitting the New Drug Application. The ACOG Executive Board went on record in 1991 supporting such an undertaking and it has not been an easy process and we applaud the courage of the Population Council as well as all of the individuals who have been involved in this difficult and important work.

The research on mifepristone will in the longer

run touch the lives of women in many different ways, many different medical situations not connected to abortion as well as connected to abortion.

ACOG believes there has been adequate testing of mifepristone with misoprostol to establish both its efficacy and safety for FDA approval. This is a well tested widely used regimen in many other countries. Over 150,000 women have used this technique for medical termination of pregnancy.

The data on the efficacy of this method for pregnancy termination that were reported to the advisory committee this morning are convincing. The recently published studies from France indicate that this is close to 97 percent successful in terminating a pregnancy up to 49 days and the failures, as you have heard, include ongoing pregnancy in less than 1 percent, incomplete abortion in less than 2 percent of subjects.

This method is safe and well tolerated by women. You have heard the data regarding the rates of adverse events and the complications. It is important to understand that the rates of severe complications, particularly prolonged bleeding or hemorrhage, is very low. Also, I think that we combined adverse events with symptoms and I want people to be clear that those are not always the identical thing although they tend to be presented

simultaneously in this setting.

The primary side effects of cramps and bleeding, which are most related to the prostaglandin part of the treatment, are similar to the symptoms of spontaneous abortion or miscarriage and tend to be brief in duration for most of the subjects. The nausea and vomiting that is also reported as an adverse event is usually very brief and easily tolerated.

During the trial we were measuring the duration of these symptoms in minutes with patients reporting symptoms that might last 10 or 15 minutes and I think that might be missed when we are all worried about making sure that we adequately account for these sorts of symptoms.

The approval of mifepristone in the U.S. will increase the ability of safe and legal early abortion and provide more options for women. The regimen will be used in physician's offices and provide women with a more private option than outpatient surgical abortion.

The availability of mifepristone also has the potential, because of its privacy, to provide greater safety from violence and harassment for both patients and providers.

ACOG looks forward to working with advances in health technology as they make the drug available to physicians.

The protocol for the use of mifepristone, including the three visits with an observation period, provides a unique opportunity for patient education and counseling. At our clinic at Columbia Presbyterian during the trial women patients were receptive to this counseling. Most of the patients left their final clinic during the trial with a highly effective long term method of contraception they intended to use. I believe the availability of mifepristone may help prevent subsequent abortions in women who choose to utilize this technique.

Mifepristone clearly may have other uses that will be beneficial to the health of women and to men and it is important these potential benefits be explored. The approval of the drug will hasten investigation of its potential use for other health problems including cancer, endometriosis, labor induction --

[Beeper sounding.]

Okay.

[Laughter.]

Let me finish by saying United States women should not be denied safe and effective options for reproductive health care, particularly the ones that are now available in at least four other countries. It is vital the important decisions about women's health be made between women and their doctors and on the basis of safety,

efficacy and what is the best for each individual woman. Thank you.

DR. CORFMAN: The next speaker is Rebecca Lindstedt for the American Life League.

American Life League, Inc. - Rebecca Lindstedt

MS. LINDSTEDT: Good afternoon. My name is Rebecca Lindstedt and I am the Director of Communications for American Life League. ALL has no conflicting financial interests in today's meeting.

American Life League is an educational pro-life organization representing over 300,000 Americans committed to the sanctity of human life. We actively oppose abortion, infanticide and euthanasia, as well as other threats to innocent human life, threats which reduce human beings to problems to be solved rather than recognize all human beings as people to be loved.

On behalf of American Life League I would today urge this panel to seriously consider the effects of recommending mifepristone to the FDA as a safe and effective drug. I would then urge this panel to reject such a recommendation.

American Life League's first and foremost objection to the approval of RU 486 is the fact that it kills an innocent human being. The abortifacient(?) "effectiveness" of RU 486 is strictly limited to the babies

gestational age. At 7 weeks, the latest age at which RU 486 can be used to cause an abortion, we are looking at a tiny pre-born child who is doing amazing things. The child's heart has been beating since the third week of development. The face, forehead, eyes, nostrils and mouth are all evident, if not distinct, as are the babies tiny ears. The head is still very large in proportion to the body but if this baby continued to grow at the same rate it is growing right now for the rest of the pregnancy it would weight two tons at birth.

Despite the familiar characteristics I have just mentioned I would point out that it is technically irrelevant. Even at fertilization or at two weeks gestation the pre-born child looks exactly as a human being is supposed to look at that particular point of development. RU 486 is a human pesticide and yet the FDA is considering its approval.

Certainly this drug violates the mandate of the Food and Drug Administration to uphold the health and welfare of Americans through safe drugs. The FDA should not approve a drug that is deadly to babies and damaging to women's health.

After only 10 months of clinical trials with RU 486 in Iowa the principle investigating gynecologist of Planned Parenthood of Greater Iowa remarked lively of the

abortion pill, "It is just so easy and so safe. It is truly a miracle." I doubt that the woman from Waterloo, Iowa, who lost nearly half of her blood and almost died would say that RU 486 was easy or safe, in fact the only miracle for her is that she is alive at all and yet this complication was never made public by Planned Parenthood of Greater Iowa.

Linette Dumbel is co-author with two other pro-abortion feminists of a book called RU 486, Misconceptions, Myths, and Morals. In the book the author has challenged the uncritical promotion of RU 486 prostaglandin by women's groups. I quote, "We do not understand why a feeling of embattlement over abortion has turned so quickly into accepting the claims for RU 486 and why the need for feminist coalition has translated in joining with many population groups that have had a history of promoting dangerous and debilitating drugs, devices, and public policies for women. We believe there is pressing need for independent feminist research, analysis, and discussion of RU 486 that does not uncritically accept the conclusion of the drug company's research."

It seems that women's health is being side-stepped to promote abortion at any cost. Pregnancy is not a disease and a baby is not a tumor. If the FDA is truly concerned about women they will reject this drug out of

hand as well as any other drug that purports to advance women's health by killing their babies. Thank you.

[Single Applause.]

DR. CORFMAN: The next speaker is Dr. Paul Jung of the American Medical Student Association.

American Medical Student Association, Paul Jung, M.D.

DR. JUNG: Good Afternoon. I am Dr. Paul Jung, Legislative Affairs Director for the American Medical Student Association. The American Medical Student Association or AMA is the nation's largest, oldest independent medical student organization, representing nearly 30,000 members from medical schools across the country. We represent the attitudes of medical students and physicians-in-training. As future physicians, we have a strong interest in the emerging health care environment in which we will practice.

Our organization's goals include improving health care and medical education. We believe that the issue of mifepristone as a method of medical pregnancy termination is significant. We commend the FDA for taking the initiative in studying the issue.

The American Medical Student Association believes strongly that voluntary abortion be legal and fully accessible to all women. We believe that this decision is

a medical decision to be made between a patient and her physician. And, we believe that voluntary abortion must be provided by sound medical or surgical methods. AMA believes that mifepristone qualifies as a safe and effective means of pregnancy termination.

Mifepristone has been used by thousands of women worldwide. This method of pregnancy termination has been found to be both safe and effective during the first weeks of pregnancy.

When compared to surgical abortions, which can only be performed after the first seven weeks of pregnancy, mifepristone is non-invasive, has a decreased risk of infection, and does not require anesthesia. In addition, mifepristone has fewer side effects and is easier to use when compared to the current "morning-after" pill.

Because mifepristone can only be used, and will only be effective, during the very early stages of pregnancy, we recognize that this drug will not replace the need for surgical abortion. Surgical methods of pregnancy termination must remain an option for women.

However, women may prefer mifepristone over surgical procedures because it is administered in a pill form. It is more private, has less side effects, and allows greater control over the termination of pregnancy. In addition, preliminary studies show that this drug may

have other therapeutic uses, for example, as a treatment for breast cancer, meningioma, endometriosis, Cushing's Syndrome, and uterine fibroma.

Based on the scientific evidence it is clear that mifepristone is a safe and effective drug which should be made available in the United States. The American Medical Student Association believes that for these reasons mifepristone should be legally available to all women immediately. Restricting mifepristone infringes on our future ability as physicians to provide the best care for all of our patients.

Policy regarding medical services should be made by sound medical evidence and not by political pressure. I, and the 30,000 medical students I represent, urge the FDA to make mifepristone available to American women. Thank you for allowing me to discuss the safety and efficacy of this drug.

DR. CORFMAN: The next speaker is Dr. Diana Dell from the American Medical Women's Association.

American Medical Women's Association - Diana Dell, M.D.

DR. DELL: Good afternoon. I am Diana Dell. I speak on behalf of the American Medical Women's Association and my own department at Duke University Medical Center. We strongly favor mifepristone being available to the women

of America. We endorse its use as an abortifacient and we support continued research into other applications for this drug.

My printed testimony details several reasons favoring introduction because of time restrictions however I will address only one, the issue of wanted pregnancy.

Ongoing abortion related violence and terrorism has affected the availability of qualified abortion providers. With limited access to abortion services the number of children being born unwanted or mistimed is increasing. Forty-four percent of the births in America were unintended at the time of conception.

American women and families need access to improved contraceptive technology in order to avoid unwanted pregnancy. They need access to medical as well as surgical options for pregnancy termination and we as a nation must begin to address the fact that the level of wantedness of a particular pregnancy can directly predict the physical and emotional well being of the child produced by that pregnancy.

You have already heard testimony implying that every conception has a right to be born. With training in both obstetrics and psychiatry I would testify to the contrary.

More than half of the 6 million pregnancies

conceived each year are mistimed or unintended. Women who carry these pregnancies begin prenatal care later and receive less adequate prenatal care than women with wanted pregnancies. The fetuses are more likely to be exposed to harmful substances like tobacco and alcohol. The child produced by an unwanted pregnancy is at greater risk of being born low birth weight and of dying within its first year. The mother is at greater risk for depression and physical abuse, the relationship with her partner is at greater risk for break-up. Both parents may suffer economic hardship and may fail to achieve their educational and career potentials.

European studies of children born to mothers who had been denied abortion found children who were less well adjusted socially, received psychiatric care more frequently and were more likely to be listed in the criminal registers. The difference between these children and carefully matched controls was still measurable by age 30.

Recent studies in New York are similarly disturbing. Before two years of age these children exhibited higher levels of fearfulness and lower levels of positive affect. In pre-school they had lower verbal developmental scores than controls.

Unwanted or mistimed pregnancies have higher

rates of physical abuse and neglect, they are more likely to be impoverished, they are more likely to be raised by a single parent, usually female, they are more likely to drop out of school. All of which means these children absorb a disproportionate share of the financial resources allocated for physical and mental health as well as resources allocated for social interventions.

Mifepristone would allow women a measure of privacy, personal dignity, and bodily integrity not currently available in this country because it can be used earlier in pregnancy and does not require surgical intervention. It should reduce violence between both patients and personnel in reproductive health centers.

In many communities, especially under served ones, mifepristone would allow citizens carrying unwanted, mistimed or abnormal pregnancy access to abortion services that are not currently available to them. We strongly urge approval for this drug now. Politics must not be allowed to take precedent over public health on this vital issue. Thank you.

DR. CORFMAN: Our next speaker is Dean Allan Rosenfield for the American Public Health Association.

American Public Health Association - Allan Rosenfield, M.D.

DR. ROSENFIELD: Thank you, members of the

committee. It is a pleasure to be here. I am Allan Rosenfield, Dean of the Columbia School of Public Health, Professor of Public Health in Obstetrics and Gynecology, a Fellow of the American College of OB/GYN, former chair of the Executive Board of the American Public Health Association and President-elect of the Association of Schools of Public Health. I appear today on behalf of the American Public Health Association.

I appreciate the opportunity to testify in favor of the approval of the anti-progestin mifepristone. Based on the evidence of its safety and effectiveness and on its potential to contribute to the health and well being of women.

This review is particularly important because if mifepristone is approved for use by the FDA it will be the first approved medical abortifacient to become available to American women.

I will not review the scientific evidence in support of this drug since this was so well covered during the morning session, rather, I will focus on some of the implications for American women if there is indeed FDA approval.

Mifepristone will provide a welcome option for those women who discover their pregnancies early and do not wish to be pregnant for whatever their personal reason.

The data are clear that mifepristone used in conjunction with an oral or vaginal prostaglandin is 96 percent effective in terminating pregnancy during the first 7 weeks of pregnancy.

Many women who have experienced both mifepristone and conventional first trimester section abortions prefer this method. In 1 study 77 percent would choose mifepristone again if faced with the need.

Based on small studies it is felt that many American women view access to a medical abortifacient taken privately as a dramatic advance for several reasons. First, harassment of patients outside abortion facilities continues and is of consequent inhibiting factor making a woman's visit to many of these facilities an emotionally trying experience at best.

In addition, fewer numbers of physicians are willing to provide surgical termination of pregnancy, primarily in view of the harassment and some times violent protests by anti-abortion groups and individuals.

Mifepristone will allow physicians more privacy in the sense that they may be able to provide the drug in their offices rather than in specially equipped clinics or hospitals, making it more difficult for those opposed to abortion to find and harass them and their patients.

Second, the difficulty of obtaining conventional

abortion is compounded by a dearth of provider sites. Approximately 80 percent of U.S. counties do not have an abortion provider or facility and many women in the United States have to travel over 50 miles to have an abortion procedure. This difficulty situation may be alleviated somewhat by the availability of a medical means of terminating the early pregnancy in which there may not be the need to restrict the drug's use to selected clinics.

I believe that with careful and complete counseling about expected side effects and potential complications mifepristone can be made available safely in a private doctor's office, assuming that there is ready access for treatment of surgical complications when necessary.

Third, as in most medical interventions a non-invasive procedure is preferable to many people to an invasive one. Use of this drug represents a lesser physical and emotional undertaking for a woman than the surgical procedure, at least for some women.

With mifepristone the risk of post-abortion infection is decreased as are other potential complications. On the other hand, there are symptoms, including nausea, cramping, and bleeding over a longer period of time with mifepristone as compared to early surgical procedures but a woman, once educated about the

alternatives, is then able to make the choice of the best procedure for her.

In Great Britain, Sweden, China, France, and elsewhere, more than 150,000 women have used this method of pregnancy termination since it first became available. One can assume in the United States many women will also choose this method.

Pregnancy diagnosis has become progressively early, rapid, and reliable, allowing women to make an informed choice at this time. I appreciate the opportunity to express my view on behalf of APHA in recommending the approval of mifepristone for general use in this country. Thank you.

DR. CORFMAN: The next speaker is Olivia Gans from the American Victims of Abortion.

American Victims of Abortion - Olivia L. Gans

MS. GANS: Thank you and good afternoon, ladies and gentlemen. My name is Olivia Gans. I am the director of American Victims of Abortion, a national organization developed by women like myself who have suffered the aftermath of surgical abortion decisions. I have held this position for over 10 years in the United States and have addressed this issue in all 50 states. In addition to my work here in America I have worked with women and professionals to establish similar support programs in 15

other countries.

I did have a surgical abortion in 1981 and I know all too well the grief, anger, and pain which defined my personal experience with abortion. I am also accustomed to having those feelings and memories ignored by those who support legal abortion. However, after 12 years of involvement with women throughout our own country and abroad I have learned that my experience is not unique.

Abortions performed using RU 486 have already produced evidence of having effects similar to those of surgical abortions, although good long-term studies are not yet available. Emotional difficulties following abortion are well-documented. Several long-term studies of women who have had abortions indicate that there are a wide range of emotional repercussions that effect women often as long as 5 or 10 years following their abortions. These emotional repercussions include intense grief, guilt, and pain.

However, the particular method of this particular abortion, RU 486, associated with chemical technique abortions provides a different set of experiences that may create a different and possibly more troubling pattern of negative reactions. When women are aware that the abortion they are having causes them to participate in the deaths of their own children they often feel more pain and guilt.

Any patient, therefore, who sees the results of the abortion, that is the developing child, is more apt to suffer than others. This is one reason why women who have late term abortions are traumatized more significantly since they will see a fully developed baby.

With RU 486 abortions it is important the woman identify the results of the abortion. She must look at these results. Seeing her dead child could be and can be traumatic. Even abortionists like Dr. Judy Tyson of Planned Parenthood of New England have reported that patients are "somewhat shocked at the tissue they passed." Thus, the very "privacy and control" which is used to sell RU 486 may actually lead to greater trauma.

In a surgical abortion the woman generally does not see the baby. Women taking RU 486 see our aborted children. Newsweek spoke of "Sarah" who saw her baby swirling around in the shower drain; and "Becky" who kept talking about her baby's little fists. There have been similar accounts in Time, the Boston Globe, the Des Moines City View, and Health magazine. There is little doubt among those of us who work with post-abortion peer support groups that a woman who takes, by her own hand, the RU 486 drug cocktail which will kill her child could experience an emotional backlash of enormous proportions.

Women in peer support groups around the world

share stories of nightmares and flashbacks to surgical abortion experiences which they cannot erase. Given the horrible dreams that are commonly experienced by women like myself who have experienced surgical abortions, one can only shudder to think what nightmares will someday visit those of us who actually see the tiny emaciated bodies of our aborted children.

Women who have surgical abortions speak of physical pain during the abortion as well as after. They complain of humiliating treatment from facility personnel and degrading responses to our request for need for more information. We are afraid o;that the already careless treatment women receive in abortion facilities across America will only worsen with the approval of RU 486.

Common theses of alienation and isolation are reported in our peer support groups and there has been little encouragement for us to speak publicly about the pain we believe is associated with our surgical abortions. Why any more so with RU 486? In fact, most of us have felt silenced for years following our abortions. will RU 486 only serve to close the circle of isolation and silence that surrounds so many women, particularly I suppose the women in these trials?

Therefore, I today urge this committee, on behalf of the thousands of women who have already struggled with

complications from abortion, to reject this drug, to disapprove it, and to make sure that American women are granted safety and security in their medical treatment. We are not guinea pigs and we and our children deserve truly life giving alternatives to abortion. Thank you very much.

DR. CORFMAN: The next speaker is Dr. Joel Brind of Baruch College.

Joel Brind, Ph.D. - Baruch College

DR. BRIND: Good afternoon. First I wish to make clear that this is not a policy statement on behalf of Baruch College but rather a summary of my research findings as a member of its permanent full-time faculty and I am here at my own expense.

In the three and a half years since I sent Commissioner Kessler a detailed letter summarizing the research literature on abortion and breast cancer considerable additional data have been gathered, bringing the issue into much sharper focus. To date a total of 30 published reports describe 24 separate epidemiological studies which give specific data on induced abortion and breast cancer incidence. Nineteen of the 24 report overall increased breast cancer risk, 12 with statistical significance.

Several important conclusions can be clearly drawn based on this substantial body of worldwide knowledge

which dates back to 1957. One, only induced abortion, not spontaneous abortion, is consistently linked to the incidence of breast cancer. The biological basis of this difference is also clear. Most spontaneous abortions are characterized by subnormal ovarian estradiol secretion. It is the surge of estradiol early in a normal pregnancy which provides an estrogen over-exposure by which most known risk factors increase breast cancer risk.

Two, induced abortion increases breast cancer risk independently of its effect in delaying first full-term pregnancy and early full-term pregnancy decreases breast cancer risk since induced abortion also abrogates this protective effect it raises breast cancer risk in two ways for young nulliparous women.

Three, the increased breast cancer risk attributable to induced abortion cannot not be explained by response bias in case controlled studies. The only study claiming to provide direct evidence of response bias relies on the specious conclusion that breast cancer patients report having had abortions that never took place and the only other study using prospective data found a statistically significant 90 percent risk increase.

Four, there is now evidence of a particularly strong interaction between induced abortion and family history of breast cancer, shown by 2 studies published in

1994.

Five, there is no basis for assuming that the somewhat younger average gestational age of medically induced abortions will confer any less of a breast cancer risk increase than surgical abortion. Neither of the two studies which looked at the timing of first trimester induced abortions found a significant difference between abortions before versus after nine weeks, endocrinological evidence backs this up, estradiol begins to surge measurably within a few days after conception.

Unfortunately, the time allotted today does not permit reporting specific data but I have complete, along with colleagues at Penn State Hershey Medical Center, a comprehensive review and meta-analysis on this subject, although it is subject to embargo until its publication in October. I can make copies for the FDA if they would like to look at them.

It brings us to the issue at hand today. In a drug approval process to date for mifepristone misoprostol has breast cancer even as a potential risk factor ever come up? Indeed, the overall highly significant positive association between induced abortion and breast cancer, which we have documented in the meta-analysis, demands that women be warned at the very least. Such warnings are already mandated to be given to women considering abortion

by law in Louisiana, Montana, and Mississippi, with more such laws in the pipeline.

Finally, we are not speaking here about any concern about the life of any fetuses, only about the life and health of the women who may be able to take these abortifacient drugs. However safe this drug regimen may appear in short term testing there is too much hard evidence that in the long term many thousands of women will get breast cancer because they took these drugs.

If this agency can simply approve, as the Population Council has requested, the legitimate use of such drugs by healthy women in order to achieve elective medical results then we will have witnessed in effect the end of the FDA as we know it, for this agency will have abandoned its function to protect American women from purveyors of harmful medicine. Thank you.

DR. CORFMAN: The next speaker is Randy O'Bannon who is speaking on behalf of Dr. Charles Cargille as a private citizen.

Randy O'Bannon, speaking for Charles Cargille, M.D.

MR. O'Bannon: My name is Randall K. O'Bannon. I am the Director of Research for the National Right to Life Educational Trustfund. I have been asked by Dr. Charles Cargille to read his statement regarding "RU 486 Long Term

Health Risks for Mother and Child."

"I wish to greet the Advisory Committee and my former colleagues, Dr. Corfman and Dr. Bardin.

It was my privilege to serve at the NIH and at the FDA. Currently I am Assistant Professor of Clinical Family Practice in New Orleans and President of the International Population and Family Association.

My statement concerns:

1. Long term health risks for mothers taking RU 486.

2. Risk of malformation and injury to babies who survive chemical abortions.

3. Risk to mothers' oocytes from RU 486.

Concerning health risks to mothers:

- Long term safety studies are lacking.
- There are over 29 potent pharmacological effects of RU 486 upon mammalian reproduction. (That is available in the appendix passed out to the committee and is available to anyone else that is interested.)
- Foreign data derives from populations not characteristic of the U.S.
- Post-abortion Syndrome has not been studied following RU 486.
- Surgical abortion has been linked to child abuse. These studies are lacking for RU 486.

- Breast cancer has been linked to surgical abortion. These studies are lacking for Ru 486.

- Psychosocial consequences of divorce and violence are linked to surgical abortion. These studies are lacking for RU 486.

- Deficiencies in maternal behavior follow surgical abortion. These have not been studied for RU 486.

- Facilitating abortion will reinforce the mentality which encourages promiscuity, teen pregnancy, and infidelity, undermining family structure and predisposing to violence and injury.

- Infectious complications may result in tubal pregnancy and sterility.

- Repeated use of RU 486 in serial abortions may increase the risks in every successive abortion.

<u>Concerning risk of malformation of babies who survive RU 486</u>:

- Numerous malformed infants are reported following prostaglandins.

- Prematurity may result from cervical softening and dilation. Such data are lacking.

- Information about neurological, IQ, and psychosocial characteristics of RU 486 abortion survivors is lacking.

- CNS effects in animal studies are proven.

Such critical data for humans is lacking.

▒ Data about any carcinogenic effects of RU 486 in abortion survivors are lacking. (Is RU 486 another DES?)

▒ The same for reproductive effects, and behavioral effects. (Will RU 486 babies resemble cocaine babies?)

Concerning risk to the mother's entire population of oocytes:

▒ High concentrations of RU 486 are measurable in follicular fluid.

▒ Could the mother's fertility be damaged along with her oocytes?

▒ Could later babies show genetic damage?

▒ Shouldn't clinical trials answer these critical questions?

▒ Shouldn't the informed consent mention these long term risks?

In conclusion:

▒ Pregnancy is not a disease.

▒ Chemical abortion is not therapeutic for the mother.

▒ RU 486 is not therapeutic for the child. (The doctor's second patient.)

▒ The benefits are unproven.

▒ The hazards may be disastrous.

▒ The Hippocratic oath on abortion should be upheld.

▒ The New Drug Application should be denied.

Thank you." Charles M. Cargille, M.D."

He listed in appendix 29 documented or suspected pharmacological actions of RU 486. I mention just a few:

1. Interference with pinopod function.

3. Disruption of folliculogenesis.

5. Decreased intracellular calcium.

12. Altered release of androgen.

17. Altered serum estrogen profiles.

23. Disruption of sexual development in rat embryos.

26. Reduced perivascular decidual cell hemostasis.

27. Degradation of endometrial extracellular matrix.

29. Inhibition of steroidogenesis.

Thank you.

DR. CORFMAN: Our next speaker is Janet Benshoof speaking for the Center for Reproductive Law and Policy.

Center for Reproductive Law and Policy - Janet Benshoof, J.D.

MS. BENSHOOF: Good afternoon. My name is Janet

Benshoor, and I am an attorney and the president of the Center for Reproductive Law and Policy. The Center's primary goal is the preservation and advancement of the Constitutional right to privacy.

Though a bit overdue, the approval of mifepristone will be an historic moment for American women. With approval of mifepristone American women stand to make immeasurable gains in reproductive choice and protection of their privacy. The approval of mifepristone will give American women access to the same medical advancement that has already been used by women in other countries.

Women with limited access to abortion providers should gain increased ability to exercise their Constitutional right and the non-invasive procedure by which mifepristone is administered heralds innumerable advances in the protection of the right of privacy.

The approval of mifepristone has the potential to provide greater privacy in several ways. First, many women encounter aggressive anti-abortion protestors when they go to known abortion providers. The unnerving quality of that experience, coupled with undergoing a profoundly personal experience is a disruption of privacy that can be circumvented when mifepristone becomes an alternative to surgical abortion.

The approval of mifepristone hopefully will give

many physicians who presently do not perform abortions, be it for lack of training in the procedure or fear of becoming a target of activists, the ability to make abortion available to their patients by learning the new protocols and follow-ups.

This new avenue for ending a pregnancy offers women the opportunity to go through this personal process with a physician with whom they have established a relationship, allow women and guard their privacy more effectively than before.

The administration of mifepristone by local physicians also holds forth the promise of removing a significant obstacle for many women who decide to end their pregnancies.

In many states having an abortion means traveling at least an entire day to the closest licensed provider in the state or regional area. This could help eradicate this burden by creating more providers. Furthermore, the absences necessitated by having to travel lengthy distances may compel many women to divulge the reason for their absence.

The approval of mifepristone and its consequent administration by local physicians would eliminate the burdens hindering many American women's exercise of their Constitutional right to choose by protecting privacy more

securely.

The abortion debate in this country has strayed far too often from the fact that abortion is an established protected Constitutional right as pronounced in Roe v. Wade. As a court recently observed in a case in Ohio, "Since the Civil War American society has not been faced with an issue so polarizing and at the same time so totally incapable of either rational discussion or compromise as abortion."

In spite of, though in some ways because of, the bitterness of the debate this forum in which we speak today, this FDA hearing necessitates that the highest standards of neutrality be employed.

Medical ethics and science stand at the forefront of the drug approval process. The procedures by which a drug is researched, investigated, and ultimately approved as safe for distribution to the American public must at all times be governed by the unwavering principles of neutrality.

The political and bureaucratic timidity that has become emblematic of the treatment accord to the abortion issue will leave as its victim millions of American women if this committee does not reaffirm its commitment to a principle of neutrality.

Differentiating abortion and mifepristone from

any other medical procedure or allowing this procedure to be hijacked by political posturing would do serious contravention of neutrality as well as to the United States Constitution. Thank you.

DR. CORFMAN: The next speaker is Helen Donovan, speaking as a private citizen.

Helen M. Donovan, J.D., speaking as a private citizen.

MS. DONOVAN: Good afternoon. I am Helen Donovan. I do not have a conflict of interest nor a financial interest.

As an attorney who represents women who are injured and killed by abortion I am concerned that the health of women in this country will be compromised by the premature approval and marketing of RU 486 for non-therapeutic use.

It is incumbent on you to ensure that the very best testing and research occurs before a drug is approved. Reliance on foreign data is inappropriate, see our experience with thalidomide.

Reliance on a study of 21,000 American women that has not yet been reported is reckless. The devastating experience of many women with FDA approved drugs and devices, the Dalcon Shield, breast implants, and Norplant, for example, should be a warning that more care is due, not

less.

While complications do occur we should not build an intolerance for injuring a percentage of women. Effective termination does not equal safe termination. The injured women who are able to come forward will have a difficult time recovering legally. The health care provider will claim that the woman was negligent and alternatively that the manufacturer is liable. The unknown manufacturer of unknown quality control is overseas and the newly invented distributor will conveniently disappear or be free of assets.

I raise these issues because of my experience with injured women and the families of women who have died as a result of induced abortions. The same dynamic that operates in the provision of surgical abortions will occur with RU 486. The paramount operating principle of time equals money will be there as well. Shortcuts, that is negligence, will have to pay off. There will be no physician/patient relationship, there will be inadequate counseling, lack of informed consent, no opportunity for the woman to read and understand the warnings and product labeling which for Norplant is seven single spaced pages.

A negligent assessment for contraindications will also be common. There will be poor follow-up and the all too common mistake of misdiagnosis of gestational age,

which, as you know, is the key to the effectiveness of RU 486. Ninety-five percent effective in 45 days, 85 percent in 63 days.

What happens after 63 days or at 10 weeks? Eleven weeks? Twelve weeks? Is it safe? If not, how will accurate dating be ensured? Will the physician rely on the menstrual data alone? As physicians you realize that that would be negligent.

Would an OB/GYN be required? Or will any physician do, including those that are not skilled in pelvic examinations and estimations of gestational age or who do not have access to ultrasound?

When one confines their reliance on foreign data, the short cuts of negligence, and the vulnerable population of women who will be persuaded to try RU 486 the poor, adolescents, persons for whom English is a second language, and the uninsured, women will lose. Seldom will they be able to recover through litigation.

Will it be their fault that they did not understand the product labeling or that the date they recorded as an LMP was in fact first trimester bleeding? Will it be a teenager's fault that she can not make a distinction between a range of side effects and complications that require immediate medical attention?

Is it possible to recommend approval when all of

the known dangers and those that could be discovered with reasonable care have not been reported?

If you do recommend approval will you ensure that the labeling protects women and not the manufacturer and providers?

Let's not wait until thousands of women have been injured and scores have filed lawsuits before we demand a commitment to accountability. It is your duty to ensure that this drug is in fact, not opinion, safe enough for the women of America. Thank you.

DR. CORFMAN: The next speaker is Grace Hsu, speaking for the Family Research Council.

Family Research Council - Gracie S. Hsu, M.H.S.

MS. HSU: Hello. My name is Gracie Hsu. I am with the Family Research Council, a nonprofit research and educational organization. My background is in public health and a policy analyst there.

The first principle of the Hippocratic Oath is to do no harm. This is the oath that physicians take in recognition of the fact that the high call of the physician is to heal and not to harm. In the same way the FDA as an agency has a responsibility, a moral duty if you will, to ensure that any drug that comes out on the market for U.S. consumption has met every possible standard to ensure safety and efficacy.

However, the abortion drug, RU 486, does not meet these high standards. First of all, this has been an approval process which has compromised its standards. Shortening the time frame for the clinical trials to a mere six months with a follow-up of only two weeks when bleeding can last for over a month is not only inadequate and insufficient to warrant approval it is a travesty that such so-called evidence would be held up as proof that this abortion drug is safe and effective enough to be thrust on the general population of U.S. women.

Furthermore, it is troubling that the U.S. data has not been presented in an adequate manner. It has not undergone thorough analysis by the FDA and I think that we -- and the fact that the U.S. data has not been looked at is problematic because U.S. women do differ from European women. First of all, the U.S. population is not homogeneous as in these different countries stated. Also, we cannot ensure compliance.

Even the clinical trials where compliance was necessary here in the U.S. is not necessarily a realistic reflection of the U.S. population as a whole where compliance is a problem. Will American women use RU 486 and suffer these effects of non-compliance? What other types of things will cause women to be put in danger?

Furthermore, the FDA has an ethical duty not to

approve a drug that will be harmful to the mothers. We already know that at least one woman in Iowa lost so much blood as a result of taking RU 486 that she almost died and there are other issues regarding the abortion drug's safety and efficacy. For example, if the drug fails to result in a complete abortion, whether due to drug inefficacy or failure of the woman to comply to the protocol, the medical complications could be severe, infection, sterility, or giving birth to a deformed baby.

There is also a dangerous void of research about the long term effects of RU 486. France has only used this since 1989 so we do not know what long term effects there are. Also, we do not know the future fertility of women, how that will be affected, the possible link with breast cancer, and the medical complications resulting from the drug's accumulation in the body.

Now, this last point is especially interesting because in the U.S. 40 percent of the 1.5 million abortions that take place every year are repeat abortions so we do not know what effects this accumulation will have.

You have heard today that you should place women's health over politics, I wholeheartedly agree. The rush to push RU 486 now without adequate data, without the analysis on presentation of U.S. data shows that there are more questions to be answered and the FDA should not

approve RU 486 at this time. Thank you.

DR. CORFMAN: The next speaker is Eleanor Smeal, speaking for the Feminist Majority Foundation.

Feminist Majority Foundation - Eleanor Smeal

MS. SMEAL: Thank you. I am Ellie Smeal, President of the Feminist Majority Foundation. For some 26 years now I have been working for women's rights and women's equality. I feel that these hearings today are the end for this particular episode of a long long journey.

The Feminist Majority Foundation, some 8 years ago, began its study and then campaign for the introduction of RU 486 into our country. Before we came out for RU 486 we underwent an extensive study. As many of you know, the feminist community has never been knee jerk and just automatically giving a rubber stamp to the medical community.

We have many many times questioned what the medical community and various pharmaceuticals were doing for women's health or were not doing for women's health. In fact, this is a very unusual occurrence, what is happening here today --

[Laughter.]

-- that the feminist community and every major woman's rights organization is united in asking you please to license and to approve RU 486 or mifepristone. It is

very unusual but it is as a result of a conscientious study.

When we heard about this in the news reports we though it was really too good to be true and we are basically very very suspicious people. We feel like we are on the outside of the community and that women are not in the leadership of it and so we embarked on a study. We studied all of the scientific data. We interviewed scientists and doctors all over this country and we were not satisfied with doing just that. We went to Europe. We went to the clinics there. We interviewed the women who were taking this medication.

After an extensive study we were satisfied that not only was this a break through but frankly it showed promise that it could be even greater than a treatment just for abortion and that this research should be expedited. Let there be no mistake that our study has included not just the abortifacient effects but also the promise of treating very serious illnesses for women such as progestin dependent breast cancer, meningioma, endometriosis.

We believe that the public support of RU 486 or mifepristone today is overwhelming. In fact, polls have shown that 66 percent of American women want it. Legislators in various states have passed it and have called for its introduction.

Today the Feminist Majority, because we have been in the leadership, receives calls almost daily from women who want access to medical abortion and some of them when we tell them it simply is not available in the United States are willing to travel to Great Britain at their own expense today to obtain it from the Marie Stopes Clinic which accepts American patients.

Several of the scientists asked me to submit some short statements for them. Dr. Gary Hodgen who is the president of the Jones Institute Foundation and a professor of reproductive medicine at the Eastern Virginia Medical School had planned to testify today. Dr. Hodgen was called away for family emergency but he wanted me to convey to you his conclusions about the compound's safety.

He first brought RU 486 into the United States in 1982. He has studied mifepristone extensively in both pre-clinical and clinical trials. He just simply concluded that this drug is safe for women.

Two other women, Dr. Anna Murphy and Dr. Katherine Horowitz wanted to underscore, and I am submitting their testimony, that the FDA alert was a negative symbolism for their research in breast cancer and the use of this as well as endometriosis and fibroid tumors and want desperately for you to reverse that negative symbolism because they believe it is necessary for this to

be studied and for their research to go forth in an expeditious manner. Thank you very much.

DR. CORFMAN: Thank you. The next speaker is Marie Head, speaking for the Feminist Women's Health Center.

Feminist Women's Health Center - Marie Head

MS. HEAD: Good afternoon. My name is Marie Head and the Population Council paid my expenses to come here and speak to you today.

I came here from Atlanta to share with you my successful experience with mifepristone for a medical abortion and because I believe that women want and should have access to another option for abortion.

As I am sure you can understand today this is a very private experience I have to share but I felt that it was important for me to do so.

My experience with the medical abortion was a year ago at the Feminist Women's Health Center in Atlanta. I choose this method because it could be done earlier than surgical abortion. I was 38 years old at the time. I was six weeks pregnant from the date of my last monthly period. I also have had a surgical procedure abortion about 10 years ago.

The medical abortion was safer and much less traumatic for me. I suffered minimal cramping an no nausea

or diarrhea. I felt like I was having a heavy menstrual flow with expulsion in about three hours.

I also have a son, an adult son, so I have experienced labor pains also. The contractions with the medical abortion cannot compare with the naturally experienced contractions women endure during labor.

The medical abortion felt more natural and less evasive than surgical procedure. The abortion experience in itself can be traumatic for women and it can be especially traumatic for women who have chosen abortion because of other traumatic experiences such as rape. I think that the medical abortion would certainly lessen this traumatic experience.

During my procedure I shared in the experience with another woman. She had almost identical experience to mine that day and she and I provided each other emotional support during the four hour period. During that period my vital signs were closely monitored and also a complete informed consent was completed before the abortion.

I have shared this experience with many other women, with my friends, my sisters, my mother, and other family members. I know that those women want this method. They want to have a choice for this method.

I am here today because I am pro-choice and I urge you to weigh the scientific evidence and to approve

the use of this method so that other women may have the opportunity to have the same choice. I welcome any opportunity to share my experience and answer any questions. Thank you for allowing me to speak today.

DR. CORFMAN: Dr. Gary Hodgen, I understand, is not here. We heard a brief statement on his behalf by Ms. Smeal.

The next speaker is Dr. Richard Glasow for the Life Issues Institute.

Life Issues Institute - Richard D. Glasow, Ph.D.

DR. GLASOW: Mr. Chairman, committee members, I am Richard D. Glasow, Ph.D., a consultant for Life Issues Institute, a pro-life education organization based in Cincinnati, Ohio.

I have researched and written extensively about RU 486 for over 10 years and have no financial interest in RU 486.

I have three points to make. First, I want to address a key issue that has received little notice. I will refer to mifepristone as RU 486 and misoprostol as its common name which is Cytotec.

Cytotec is licensed in the United States to prevent gastric ulcers and carries its own set of risks for women and their unborn babies, including the risk of deformities. The RU 486 abortion has, as I understand the

NDA has been proposed, requires both of those drugs. Currently Cytotec is contraindicated for pregnant women and the packaging carries very large and clear specific warnings about that.

The manufacturer of Cytotec, G.D. Searle, has publicly opposed using their drug for abortion in a letter in a March 19, 1993, Wall Street Journal.

The record of safety and efficacy presented here is incomplete. We heard and saw a lot about RU 486. Shouldn't G.D. Searle, the manufacturer of the other drug in the abortion procedure be at this hearing to present scientific and medical data about the effects of RU 486 on women and their offspring?

The citizen petition presented to the Agency in February 1995 raised medical issues about Cytotec's effects but we have seen next to nothing about that today, in fact, there has been one slide, period, end of paragraph. Cytotec has its own dangers.

Second, Cytotec or RU 486/Cytotec abortion has a incidence of serious complications, requires more visits, will probably be more expensive. So, what's the big deal? Why are we trying to put this on the market? Why the big push?

Well, it goes back to the issue that doctors do not like to do abortions. There is a stigma to being an

abortionist. That national survey that was flashed up on the screen earlier today showed that about 33 percent of obstetricians and gynecologists currently perform abortions and only 3 percent of family practitioners currently perform abortions.

Over the last decade fewer and fewer doctors are performing abortions and that worries the abortion lobby. They hope, as we have seen today, several people have referred to it, including the sponsor, that more doctors will do abortions who currently do not perform abortions because they will use RU 486 and the national survey bears that out. Among family practitioners the number of abortionists could go from 3 percent to 28 percent if RU 486 were to be put on the market but 1 point that they do not mention and is frequently overlooked is all we have to do is look back on our history in this country to Roe v. Wade and what happened after that.

It is as clear as the nose on your face, when the number of abortionists goes up the number of abortions will increase too. It will just happen. It will not just displace some surgical abortions, we will have more than the 1.5 million abortions that we have now.

Finally, my third point, is I urge you to consider whether the approval of RU 486 has to be rushed through so rapidly. RU 486 is the first abortion drug to

be considered by the Agency in over 20 years. They are asking you to put the reputation of this committee and your personal professional reputation and base your approval on incomplete U.S. efficacy and safety data.

There are many unresolved issues. For example, women will be taking two powerful synthetic hormones in this abortion procedure and we know virtually nothing about the long term effects. Shouldn't we try to avoid another DES, thalidomide, Dalcon Shield? Please vote against approval of RU 486 for abortion and protect the lives and health of women and their offspring. Thank you very much.

DR. CORFMAN: Next speaker is Marcy Wilder, speaking for the National Abortion and Reproductive Rights League.

National Abortion and Reproductive Rights League - Marcy J. Wilder, J.D.

MS. WILDER: Good afternoon. My name is Marcy Wilder, and I am the legal director of the National Abortion and Reproductive Rights League. NARRL is a national non-profit advocacy organization that has worked through the political process for 27 years to keep abortion safe, legal, and accessible for all women. NARRL has 35 state affiliates and represents 500,000 members.

Sixteen years ago mifepristone was synthesized by a French pharmaceutical company. Today it has been

approved for use in three European countries. It has been used by more than 200,000 women and clinical trials in the U.S. have been completed, yet, it remains unavailable to American women. Why?

The answer is anti-choice politics, pure and simple. Recognizing that mifepristone would expand reproductive choices and make it more difficult to target women's health clinics for violence and harassment anti-choice forces worked first to keep the drug out of the U.S. for clinical trials and then to block FDA approval.

Their opposition, from the time the drug was first introduced, has been fierce, political, and firmly rooted in an absolute and ideological opposition to abortion.

In 1988, almost immediately upon learning that mifepristone had become available in France, anti-abortion forces called for a worldwide boycott of the manufacturer. Succumbing to enormous political pressure and the boycott threat the company suspended marketing of the drug. Two days later, however, the French Minister of Health ordered the drug back on the market calling it the "moral property of women."

Women in the United States did not fair quite so well. In 1989 facing pressure from anti-choice Members of Congress and the Bush Administration the FDA issued an

import ban. A United States district court concluded, and I quote, "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."

Mifepristone provides one of many examples of how anti-choice forces have intruded into the practice of science and medicine. That interference did not start, and I suspect it will not end, with mifepristone.

For more than a decade abortion opponents have blocked promising research in contraceptive technology, in fertility treatments, human embryo research, and fetal tissue transplant research. They have impeded medical advances that could benefit the health of millions of Americans suffering from diabetes, Alzheimer's Disease, Parkinson's Disease, and other serious conditions.

Today women's health advocates are asking that the FDA apply the same rigorous review process to mifepristone that is applied to other new drugs. The law requires that the decision be based on women's health and safety, not abortion politics. The evidence strongly suggests that mifepristone is safe and effective and should be made available.

Delays in the approval process, resulting from anti-choice politics, will undermine women's health and

deny them access to what is perhaps the most important advance in reproductive health technology since the birth control pill.

American women urgently need better access to better contraceptive methods to prevent unintended pregnancy but when a woman does face a crisis pregnancy she must have access to all medically safe options.

DR. CORFMAN: Next speaker is Dr. Paul Blumenthal, National Abortion Federation.

National Abortion Federation - Paul Blumenthal, M.D.

DR. BLUMENTHAL: Good afternoon. My name is Paul Blumenthal. I am speaking on behalf of the National Abortion Federation, which has, to my knowledge, no financial interest in these proceedings.

I am a board certified obstetrician/gynecologist and associate professor of gynecology and obstetrics at the Johns Hopkins University School of Medicine and I am the medical director of Planned Parenthood of Maryland. In addition, I am an advisor to the World Health Organization, the United States Agency for International Development on issues relating to safe motherhood, contraception, reproductive health care and quality assurance.

I am here today speaking on behalf of the National Abortion Federation, the national organization of