FOOD AND DRUG ADMINISTRATION

REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy

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

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PROCEEDINGS (9.00 a.m.)

DR. DAVIDSON: May I have your attention, please.

I would like to open this meeting of the Reproductive Health Drugs Advisory Committee, considering the topic that is well-published of this agenda.

To begin with, in terms of just some internal Committee issues, I would like to note and appreciate that this is the last meeting for three of the members who are with us today: Dr. Daling, Dr. Henderson and Dr. Zones. We certainly had the professional pleasure and benefit of their participation in this committee.

This is also the first meeting of Dr. Richard Azziz, and as has been customary, Richard, knowing that you are from the University of Alabama, I am sure you will take this opportunity to distinguish which campus that is.

Welcome to the Committee.

DR. AZZIZ: I am a professor in the Department of Obstetrics and Gynecology and the Department of Medicine at the University of Alabama at Birmingham. As we always have to say, there are three campuses, of which Birmingham is the important one.

DR. DAVIDSON: We have confirmed at the last meeting, but I would please have you note the dates of the future meetings that are at the top of the agenda today.

The conflict of interest statement will be read

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day by Marina Hooten(?), who is chief of the Ethics Branch Division of Ethics and Program Integrity of the FDA.

DR. HOOTEN: Good morning.

The following announcement addresses the issue of conflict of interest with regard to the meeting, and it is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for conflict of interest at this meeting, with the following exception:

Dr. Jane Zones would like to report to reflect that she was, within the past year, a member of the Board of Directors for the National Women's Health Network, a membership-based, non-profit, public interest health advocacy organization. The National Women's Health Network is making a presentation today. However, she is not aware of what they are going to present.

Dr. Zones will be participating as a consumer representative member today, but she will not be voting with respect to this product.

In the event that the discussion involves any

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other product or firm not already on the agenda for which the FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they disclose any current or previous financial interest or professional involvement with any firm whose products they may wish to comment upon.

DR. DAVIDSON: Thank you very much.

I should indicate before we begin that in addition to the Committee members seated around the table, there are four Agency persons: Dr. Phil Corfman, who is the secretariat of the Committee, who is immediately to my right; and to the end of the table to my right, Mary Pendergast, who is the Deputy Commissioner for the FDA; Dr. Kessler, who is the Commissioner and who will speak momentarily; and Dr. Lisa Rarick, who is the Acting Director of the Division of Reproductive and Urologic Drugs, a new position and a new title, for which she is to be congratulated for.

We will begin with opening comments by Dr. David Kessler, the Commissioner of the FDA.

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Agenda Item: Opening Comments - David A. Kessler, M.D., Commissioner of Food and Drugs

DR. KESSLER: Thank you, Dr. Davidson. Good morning.

The purpose of this Advisory Committee Meeting is to examine the data from clinical trials of mifepristone, an antiprogestin drug, for the termination of early pregnancy. Antiprogestins work by blocking the effect of a hormone, progesterone. This hormone, progesterone, is necessary to maintain pregnancy.

Mifepristone acts by keeping progesterone from binding to its receptors, which results in the termination of pregnancy. Mifepristone is also known as RU-486 and has been available for this use in France since 1989, but was later approved in Sweden and the United Kingdom.

Since 1989, at least 150,000 women have used this drug. The U.S. rights to mifepristone were transferred in 1994 to The Population Council, a non-profit research organization. On March 18, 1996, FDA received a new drug application from The Population Council for the use of mifepristone in combination with misoprostol, an oral prostaglandin.

Their proposed regimen for the use of mifepristone for the termination of early pregnancy entails the oral administration of 600 milligrams of mifepristone

within 49 days of the beginning of the last menstrual period, followed two days later by oral administration of 400 micrograms of misoprostol.

The Agency formally accepted this application on the basis of foreign clinical data in the form of two large clinical trials conducted in France. FDA accepted this application with the understanding that the sponsor would, during the course of the Agency's review of the application, submit safety data from a recently concluded U.S. clinical trial.

The FDA classified this new drug application as a priority application because it is the first drug proposed for this indication. The goals set out in the Prescription Drug User Fee Act of 1992 is for FDA to act on priority applications within six months.

There are several parts to a new drug application. Our focus today, your focus today, is on the safety and effectiveness of this drug for the termination of early pregnancy. You will be reviewing the pharmacology, toxicology and clinical findings.

As usual, you will not be reviewing the chemistry and manufacturing controls information. Outstanding chemistry and manufacturing controls issues will be addressed by the reviewing division.

Your task today is to review the pharmacological,

toxicological and clinical data of mifepristone for its proposed indication, focusing on the science. You will hear presentations from the applicant and then you will hear from FDA's Division of Reproductive and Urologic Drug Products.

Two and a half hours have been set aside for open public hearing.

We will then seek your advice on the following questions:

Question 1: Do the results of the open-label, historically-controlled studies conducted in France establish the efficacy of this regimen for use in the United States? If not, what additional efficacy information should the applicant provide?

Question 2: The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials and foreign postmarketing experience. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? If not, what additional safety information should the applicant provide?

In your discussion, we would also appreciate your commenting on the following issues:

Whether the adverse events associated with the regimen can be adequately managed when the regimen is

administered as labeled and the acceptability of the frequency of adverse events.

Question 3: Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for the use of the regimen for the proposed indication in the United States?

Question 4: If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?

Question 5: If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?

Question 6: The sponsor and the FDA review staff will discuss a proposed distribution system. If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?

Question 7: If the regimen were to be approved, what recommendations, if any, do you have for postmarketing studies?

Those are the questions before you today. The issue for you to consider is the safety and effectiveness

of mifepristone for the proposed indications.

To members of this advisory committee, let me simply say what I have told other advisory committees faced with making recommendations on products where there are intense feelings and differing viewpoints. What you need to do today is to focus on the science.

Let me repeat that. What you need to do today is to focus on the science. Exam the clinical data carefully. Ask the tough questions and then give the FDA your best scientific advice based on the data.

The FDA has convened this meeting to hear from the best outside scientific advisors available. The advice is not binding on the FDA, but, of course, the agency will take it very seriously.

It is important for everyone to know that as always the FDA has been very sensitive to potential conflicts of interest among its advisory committee members. Conflict of interest issues for this advisory committee meeting have been reviewed by the advisors and consultant staff of FDA Center for Drugs, by FDA's Division of Ethics and Program Integrity, in consultation with the Office of the Special Council for Ethics of the Department of Health and Human Services and by the U.S. Office of Government Ethics.

We have carefully considered the issues

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surrounding any potential conflicts of interest and these potential conflicts have been resolved.

The bottom-line question for you today is whether ifepristone for its proposed indications is safe and ffective.

Thank you.

DR. DAVIDSON: Thank you, Dr. Kessler.

The sponsor for this new drug application is The opulation Council. The morning will be devoted to their resentation to the Committee.

I would like to indicate that though it is not oted on the agenda, at our about 11:00 a.m., we will take 15-minute break, so that the sponsor understands that, nd plan for our 15 minutes during this period from now ntil 1 o'clock.

The Division presentation will be the last hour etween 12 and 1 o'clock.

The first presenter will be Sandra P. Arnold, ice President for Corporate Affairs of The Population ouncil.

I would like that you would introduce in sequence he following presenters yourself.

Agenda Item: Presentations by the Sponsor, The opulation Council

MS. ARNOLD: Thank you.

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Good morning. My name is Sandra Arnold. I am ice President of Corporate Affairs at The Population ouncil, as you know, the sponsor of this application.

The Population Council is, as Dr. Kessler said, n international, non-profit, research institution edicated to exploring the causes and consequences of opulation growth and to improving women's and men's eproductive health.

The Council has studied mifepristone since the arly 1980s and became the sponsor of this application fter it became clear that doing so was the only way this rug would reach American women. Women in the United tates want this drug now and there is no reason to wait.

If women in other countries, notably, France, the nited Kingdom and Sweden, could have access to safe and ffective early medical abortion, we felt American women ught to have this choice as well.

To make this happen, the Council immediately went o work on filing the new drug application, arranging for anufacturing and distribution and conducting clinical rials. This work has led to today's hearing.

At the International Conference on Population and evelopment held in Cairo in 1994, the international ommunities strongly affirmed that unwanted pregnancies ould be prevented through expanded and improved family

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planning and that unsafe abortion was a major public concern worldwide. This is also The Population Council's view.

While abortion is safe and legal in the United States, access to abortion in many communities is diminishing. Women seeking legal abortion face increasingly difficult obstacles, while abortion providers and clinic staff frequently work under potentially violent and hazardous conditions.

We support the use of mifepristone as a safe medical alternative to safe surgical abortion. Medical abortion won't replace surgical abortion, but we believe that the availability of early medical abortion eventually will improve women's access to abortion services and will make those services more private.

Women will be able to obtain medical abortion at selected doctors' offices and clinics free of violence and harassment.

The availability of mifepristone will also not lead to an increased number of abortions. It hasn't done so in France, where the drug has been available since 1989, but it will expand women's options. Medical abortion is an important option. It can be provided as soon as a woman knows she is pregnant; whereas, surgical abortion must wait until later in the pregnancy.

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It avoids the use of anesthetics. It simulates a natural miscarriage and women have said that it gives them the feeling that they are in control of their own destinies. This is a safe and effective procedure, which has been used by hundreds of thousands of women outside the United States.

These are the reasons that United States women want this drug and these are the reasons that The Population Council has sponsored it.

I would now like to take a moment to introduce the people who will be presenting to you briefly.

Dr. Ann Robbins is a neuroendocrinologist at The Population Council. She has been with us for five years and she has been responsible for the mifepristone NDA.

Dr. Irvin Spitz is an endocrinologist, who has been with The Population Council for 13 years. Dr. Spitz has been involved in the clinical development of mifepristone and he designed many of the studies of pregnancy termination and other indications for this compound.

Dr. Wayne Bardin is an endocrinologist. He was Vice President of The Population Council and director of the Center for Biomedical Research for 17 years, ending in 1995, at the end of 1995. Dr. Bardin had responsibility for the oversight of this NDA preparation and he has now

1 turned to a career as an independent consultant.
2 Dr. Beverly Winikoff is a public health
3 physician. She has been with The Population Council for 18
ars. She is our program director for reproductive
health. And Dr. Winikoff has had responsibility for the
6 acceptability evaluation for mifepristone.
7 Finally, Dr. Elizabeth Newhall is a board
8 certified obstetrician/gynecologist, who for the past eight
9 years has been an abortion provider and the medical
10 director of the Downtown Women's Center in Portland,
11 Oregon. Dr. Newhall was a participant in the mifepristone
12 clinical trials.
13 I would now like to turn the floor over to Dr.
14 Robbins, Dr. Ann Robbins, who will provide some background
15 on mifepristone development and on this application and
16 will introduce the effectiveness, safety and acceptability
17 discussions.
18 Thank you.
19 Dr. Robbins.
20 DR. ROBBINS: Thank you, Sandy. Good morning.
21 We are here today to discuss the data supporting
22 the use of mifepristone and misoprostol for medical
23 abortion. Today's presentations will document that this is
24 a safe and effective method of pregnancy termination, that
25 it is accepted and desired as an alternative to surgical

ortion by American women and that it can quite feasibly
be delivered in the U.S. health care system.
3 If I can have the slides and the lights down,
4 please.
5 I would like to begin today's presentations with
6 a brief discussion of the key historical events that have
7 led to the use of mifepristone and misoprostol for medical
8 abortion, as well as to summarize The Population Council's
9 activities in bringing this method to the United States.
10 This presents some of the key developmental
11 milestones in the use of mifepristone for pregnancy
12 termination. In 1970, the progesterone receptor was
13 identified. Twelve years later, in 1982, was the initial
14 report of pregnancy termination with mifepristone,
15 demonstrated to be the first progesterone receptor
16 antagonist.
17 The following year, in 1983, The Population
18 Council filed an IND, investigational new drug application,
19 for clinical trials of mifepristone in the United States.
20 Following several years of testing, in 1988, marketing
21 approval for mifepristone was granted in France and it
22 began being used the following year.
23 In 1991, additional approval was obtained in the
24 United Kingdom and the following year, in 1992, in Sweden.
This describes some of the important clinical

1 developments of mifepristone. As I said, the initial
2 report of pregnancy termination occurred in 1982, following
3 a series of testings and dose-finding studies, with the
4 selection of a single dose of 600 milligrams of
5 mifepristone for pregnancy termination.
6 How does mifepristone work to terminate a
7 pregnancy? The next slide summarizes the key hormonal
8 events that occur during pregnancy; fertilization, which
9 occurs following ovulation and the luteinizing hormone
10 surge shown here in yellow then causes an increase in
11 progesterone secretion.
12 Implantation begins and takes a few days to
13 complete and this is accompanied by a concomitant rise in
14 human chorionic gonadotropin. Progesterone, shown here in
15 white, is essential for the maintenance of pregnancy and
16 mifepristone blocks the action of this hormone, as shown
17 dramatically in the next slide.
18 Mifepristone, here abbreviated "mif," is given
19 orally as a tablet. It works to block the action, to block
20 the progesterone receptors, located here in the decidual
21 lining of the uterus. This causes decidual breakdown,
22 which results in a sloughing of this lining and bleeding
23 and causes detachment of the blastocyst.
24 This causes a cascade of hormonal events,
25 diagrammed here, which culminate in two important

1 activities, an increase in uterine contractility and
2 cervical softening, both of which lead to expulsion of the
3 embryo. Many women compared this process to that which
4 occurs during a spontaneous miscarriage.
5 Several more years of testing showed that the
6 addition of a prostaglandin to this regime increased the
7 efficacy of mifepristone in terminating pregnancy. This
8 works in the following manner. This is the same diagram I
9 just showed you. Now, I have added the addition of a
10 prostaglandin, abbreviated here "pg."
11 The thick blue line shows that the action of
12 prostaglandin is to further increase uterine contractility.
13 This increase in contractions leads to a greater efficacy
14 in the expulsion of the embryo.
15 This regime has been tested in thousands of
16 women. The standard regime that is used in this
17 combination is diagrammed here. We have mifepristone
18 delivered on visit one. Two days later on visit two, a
19 prostaglandin is given to the women and this is followed
20 approximately two weeks later by a follow-up visit, in
21 which the confirmation of pregnancy occurs and, if not, the
22 woman is given a surgical abortion.
23 As I have said, this has been tested and widely
24 and shown to be a very safe and effective method for
25 pregnancy termination. However, there was a demonstration

of very rare but serious cardiovascular effects associated with the use of one of the prostaglandins, sulprostone, which is delivered by injection.

This led to trials on alternative prostaglandins. There were several large trials conducted in France that looked at the combination of mifepristone and the orally-available prostaglandin — orally-delivered prostaglandin, misoprostol.

The next slide shows that these studies with mifepristone and misoprostol followed the same regime I just showed you with the other prostaglandins; that is, mifepristone delivered on day one; two days later, misoprostol on the second visit. The red box here indicates the four to five hours that the remained in the clinic following the administration of misoprostol to check for any events that occur immediately after the misoprostol delivery.

And, finally, again, after about two weeks, there was a follow-up visit to confirm that pregnancy termination had occurred.

You have seen there that there is a wide variety of -- a large number of women have used this drug. I would like to now just show you some of the international experience with mifepristone. We see here that approximately 200,000 women have used mifepristone for all

rposes and the vast majority of these have occurred for ıne use of medical abortion.

This has been almost 190,000 of these women have used it for this purpose. You can see, 20,000 subjects have mifepristone alone; approximately 60,000 have used mifepristone plus sulprostone; 40,000 have used mifepristone plus gemeprost and an additional 70,000 have used the combination of mifepristone and misoprostol.

This is where we stand today. This drug has been tested in many, many countries and it has been approved, as I have said, in four, but not yet available in the United States.

I would like to now summarize the activities of The Population Council to register this regime within the United States. As Dr. Kessler mentioned, in 1994, in May of that year, The Population Council was granted the rights to the use of mifepristone in the United States. At that time, we began simultaneous work on two concurrent tracks of activity; first, to conduct a U.S. clinical trial and, secondly, to file a new drug application.

Of course, this is the focus of today's presentations and review, but I would like to give you some background on the U.S. clinical trial.

In the U.S., we have used the same regime that has been used in France; mifepristone given on day one, 600

milligrams. This is followed two days later by misoprostol, 400 micrograms delivered orally. Again, on visit two, the women stay in the clinic for four hours, where they are observed and then they return two weeks later for confirmation that pregnancy termination has occurred and if it hasn't, they receive a surgical abortion.

These are some of the key aspects of the clinical trial. The trial was initiated in the fall of 1994. We have enrolled 2,121 women. Women were enrolled for a gestation of up to 63 days of pregnancy, counted from the first day of their last menstrual period.

The clinical trial took place in 17 sites. These were geographically distributed across 15 states in this country and included women of all ethnic diversities. Secondly, they also were conducted in a variety of provider settings.

The enrollment was concluded last fall. We are currently in the process of finishing our data analysis of the efficacy results. However, we have included the safety results and they will be discussed later today by Dr. Bardin.

Today, I would like to emphasize right now, though, we can tell the Committee and the audience that this has been — there have been no adverse events,

serious, unexpected adverse events, during the course of this trial and also, as you will hear later from Dr. Winikoff and Dr. Newhall, this drug is very acceptable to United States women. We will hear those presentations later.

Now, let's look at the activities that have underlined the new drug application. In the summer of 1994, we had a pre-NDA meeting with the FDA to discuss our application. NDA preparations began. The following winter of 1994, we obtained the database for the French pivotal trials.. We began audit and validation of this database and we did a full reanalysis of the French database. These are the data that will make up the bulk of the data being presented today as they form the pivotal trial submitted in our new drug application.

In the summer of 1995 was our cutoff date for information to be included in the NDA. Throughout the fall and winter of 1995, final production of the NDA began and in the spring of this year, as you have heard, on March 14, we submitted the new drug application to the FDA.

During the summer, we submitted an additional safety update and the FDA has audited the French pivotal trial sites and the data from this trial.

For my final slide, I would like to give you some aspects of the clinical features of the new drug

application. Of course, as Dr. Kessler, our new drug application contains all the sections that you need in an NDA, but we are going to focus today on some of the inical features.

The NDA contains efficacy and safety data on the use of mifepristone alone or mifepristone and other prostaglandins for pregnancy termination. The pivotal trials included in the NDA look at the efficacy and safety data that come from the large clinical trials of mifepristone and misoprostol that were conducted in France that I described earlier.

These two French studies enroll a total of 2,480 subjects and you will hear their safety and efficacy data presented later.

In addition, the NDA contains all of the international safety data for other clinical trials, including the U.S. clinical trial and clinical trials for uses other than abortifacients, use of mifepristone during compassionate use and data from postmarketing surveillance.

We believe the data that you will hear that are contained in the NDA prove that this is a safe and effective method of pregnancy termination.

I would like to now ask Dr. Irvin Spitz to begin the discussion of the efficacy data.

Dr. Spitz.

DR. SPITZ: Thank you. Good morning.

May we have the first slide, please.

My task this morning is to review the effectiveness of mifepristone and misoprostol for medical abortion.

Next slide, please.

This indicates the various study regimens, which have been used historically. The firstly there is mifepristone alone; secondly, there were studies with mifepristone and the prostaglandins, sulprostone or geneprost and, thirdly, mifepristone and misoprostol. And the latter constitutes the basis of the clinical section of the NDA application.

Now, with regard to mifepristone alone, the first published study was by Herrmann and co-workers in 1982, and this showed pregnancy termination in 9 of 11 women, with duration of gestation of less than 56 days, following mifepristone administered in a dose of 200 milligram a day for four days.

Now, numerous studies have been performed since then and the results are essentially similar and these are shown in this slide; a total of 605 women, and in this slide and all subsequent slides, the number of subjects studied will be shown on the top of these bars.

So, using various dose schedules, from 140 to a

1,000 milligram, administered over one to seven days, the efficacy was 70 percent with a range of 50 to 85 percent.

Pharmacokinetic studies conducted with mifepristone showed that it was possible to use this agent as a single dose and the dose, which was, in fact, selected, was 600 milligram a day and in the total of 1,737 women, you will see that the same successful termination of pregnancy was 82 percent, ranging from 70 to 90 percent.

So, this was better than the original regimen, but, obviously, not adequate for general clinical use. So, the next main advance came with the appreciation of the actions of the prostaglandins. Now, it has been known since 1973, that uterine activity is controlled by a balance between the intrinsic inhibition of progesterone and stimulation by prostaglandins.

So, in an important study by Bygdeman & Swahn in 1985, they showed that mifepristone increases the sensitivity of the myometrium to prostaglandins. So, this set the stage for the next part of the development, the use of mifepristone and prostaglandins. Now, in the usual dose regimen, mifepristone is given on the first visit and the prostaglandin is given on visit two, which is about 36 to 48 hours after the mifepristone because this is the time of maximum sensitivity of the uterus to the prostaglandin. Then there is always a third visit after 14 days to

determine if pregnancy termination did occur.

Now, what are the types of prostaglandins which have been used? Basically, there are three types. It was first sulprostone, a PGE2 analogue, given parenterally, which requires refrigeration, is an expensive preparation and is not available in this country.

The second was geneprost. This is a PGE1 analogue. It is given as a vaginal suppository. It also requires refrigeration, is an expensive compound and is not available in this country. Then, thirdly, we have misoprostol, a PGE1, orally-administered analogue available in 45 countries, available in the United States. It does not require refrigeration and is relatively inexpensive.

So, this was the compound, in fact, which has been used in the U.S. studies.

But, first, let us review the studies with sulprostone or geneprost. In fact, this slide summarizes the results from the literature review in women with duration of gestation of 49 days or less with these prostaglandins. With sulprostone in over 15,000 women who have been enrolled, the success for medical abortion occurred in 95.7 percent and with geneprost in over 2,000 women, the successful termination of pregnancy in 95.5 percent.

So, these were very acceptable results and you

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can contrast it in the bottom panel with the use of mifepristone alone, where the success, as I have shown you before, was only 81 percent.

Now, the use of sulprostone was associated in approximately 1 in 20,000 women with some adverse carotid effects and this is now no longer used. The prostaglandins, which, in fact, are still used today are gemeprost and misoprostol.

As I mentioned before and you have heard from the Commissioner and from Dr. Robbins, the focus of this NDA application is mifepristone and misoprostol. This forms the basis of the two clinical studies conducted in France, which are being used to support this NDA application.

Now, what were these two critical pivotal studies? I am calling them Study 1 and Study 2. Now, Study 1 comprised women with a duration of gestation of 49 days or less and there was a slight difference in Study 2. This included women with duration of gestation of 49 days or less. But there was also another cohort of women with duration of gestation of 50 to 63 days.

So, that represents one slight difference in these two studies. In both studies, mifepristone was administered in a dose of 600 milligram on visit one and misoprostol was given in a dose of 400 microgram on visit two. And the women were then observed in the clinic for

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three hours.

Now, in Study No. 2, those women, who had not had medical termination at three hours, were then given an extra dose of 200 micrograms of misoprostol, shown in the green, an extra dose, and they were observed for a further two hours in the clinic.

Then the subjects went home and there was a third visit conducted after two weeks to determine the results of pregnancy termination. So, basically, two fundamental differences; duration of gestation, 49 days and the second study 49 or second cohort, and in the Study 2, also, an additional dose if there was no medical termination of pregnancy after three hours.

So, now, I am going to review some of these aspects. I am going to now review the effect of this extra dose of misoprostol. Then I am going to review the efficacy of this regimen, considering -- and I will only review the efficacy in women with duration of gestation under 49 days, which forms the basis for this NDA application.

And subsequently, Dr. Bardin will review the safety data of all these studies, including women with duration of gestation up to 63 days. So, the first question which we have to resolve, what is the potential effect of the second dose?

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Firstly, just to show you some of the numbers, total number of women enrolled, 1,286 in Study 1; 1,194 in Study 2, a total of 2,480 women who were enrolled. The number of women with gestation of 49 days or less, 1,089 in Study 1; 492 in Study 2, and a total of 1,681 women.

Then number of women with gestation of 50 days or more, there were 628, and the vast majority, as I have explained were in Study 2.

Now, let us work out the effect of this second dose of misoprostol and, in fact, this bar graph shows the outcome analysis of women, who received misoprostol with a duration of gestation of 49 days or less; again, Study 1 or Study 2.

Now, these green bars over here shows the percent, which is on the vertical axis, the percent of women, who had medical termination of pregnancy by three hours in both groups. And it was the same in both groups; 36 percent or 37 percent in both groups. So, in both groups by three hours there was a termination of pregnancy of 36 percent.

Now, these other subjects, all these other women in Group 2 were then given the second dose of misoprostol and now, let us compare the results for Study 1 and Study 2. In the turquoise, you see the number of women who had abortion after three hours and, again, in the two groups,

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the results are identical. The top blue bars shows those women who had unsuccessful termination of pregnancy and the numbers are similar.

So, in fact, you will see that the results are identical, whether the women had a single dose of misoprostol or the extra dose. This is the justification. This is the justification for integrating the results together. In fact, this is shown in this slide over here.

In this total of 1,681 women with a duration of gestation of 49 days or less, there was complete medical termination of pregnancy in 95.5 percent of the women, 95.5. percent. What were the reasons for failure of medical termination of pregnancy in these 1,681 women? Well, in 1.3 percent, there was a continuing pregnancy, which was then terminated by a D&C or vacuum aspiration. In 2.9 percent, there was an incomplete abortion and in 0.3 percent, the women required dilatation and curettage or vacuum aspiration for bleeding.

What we have also attempted to do over here is to show the time of expulsion after misoprostol in these women with duration of gestation of 49 days or less. On the vertical axis, you see the percent of women with an expulsion at different time intervals; 0 to 3 hours, 3 to 4 hours, 4 to 24 hours and greater than 24 hours.

You will see that during the time of observation

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in the clinic, which was from 0 to 3 and up to 4 hours, 54 percent of the women had termination of pregnancy within the time while they were in the clinic. In fact, a further ? percent had termination of pregnancy up to 24 hours, which indicates that over three-quarters of the women had medical termination of pregnancy by — to the end of 24 hours and only the remaining 8 percent on the data which we have had medical termination of pregnancy after 24 hours. So, this is the effect of the time of expulsion.

Now, we have also tried to determine the effect of certain patient characteristics, which could determine the efficacy results. What did we look for? We have looked at age. We have looked at height, weight. We have looked at body mass index. We have looked at gravity. We have looked at parity. We have looked at the number of previous abortions and we have also looked at the duration of gestation.

Now, it turns out that there are only two basic characteristics, which influence the efficacy of the regimen. And these are the duration of gestation and the age of the patient. Now, what about the duration of gestation? Well, the predicted probability, the predicted probability of complete medical termination in a woman of 35 days duration of pregnancy is 97 percent and in a woman with duration of gestation of 49 days, this is still high,

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it it decreases to 92 percent.

So, women with a shorter duration of gestation have a better response than those with the longer duration of gestation. There is also, as I mentioned, a strong interaction between chronological age and gestational age. If one then takes women, say, at 49 days duration, a woman of 19, has a 97 percent predictive probability of complete termination of pregnancy; whereas, her counterpart at age 35, will only have a 92 percent predictive probability.

But I would like to stress that within the duration of gestation of 49 days and all the ages of all the women studied, the results were excellent with an efficacy of 95.5 percent.

Now, I would also now just like to put our results in international context and to summarize our results together with some of the other results from the literature. Again, 1,681 women with a duration of gestation of 49 days or less from the French pivotal studies, here is a literature review, all the women I could find from the literature, a total of 1,696 women. And I have compared this with the use of the other prostaglandin, the vaginal suppository, gemeprost, 2,186 women.

And you will see that with all these -- with our results, with the literature review and with gemeprost, the results are identical, complete medical termination of

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pregnancy at 95.5 to 96.2 percent of the women.

Now, as I mentioned before, a formal analysis of the U.S. data has not as yet been fully completed and verification of the data collected at these sites has only just been completed now. But preliminary informal reports sent to me each week by the clinics, which have not been verified, indicates that in general the results of the U.S. study conform to the same degree to that of the international experience.

So, from this, ladies and gentlemen, I would really conclude that mifepristone plus misoprostol is effective for the medical termination of pregnancy in women with duration of gestation of 49 days or less.

So, I thank you for your attention and I will call upon Dr. Bardin, who will assess for you the efficacy data.

Dr. Bardin.

DR. DAVIDSON: The Committee may have questions.

DR. SPITZ: Certainly.

DR. HENDERSON: I actually have a question of Dr. Arnold — I am sorry — Dr. Robbins.

You commented several times that if the termination was not completed after the third visit, that women were given a surgical abortion. Was that an option? How did you make them have a surgical abortion? What

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options were they presented at that third visit?

DR. ROBBINS: In the trials, as part of the informed consent, as part of the inclusion/exclusion criteria, that described the protocol in detail and at that time, before they signed the informed consent, they are told that if their pregnancy is not terminated by the medical abortifacient, they will need to have a surgical abortion at the end of their follow-up visit at week two.

So, they are counseled this prior to signing their informed consent and they sign the informed consent understanding that. Of course, we can never force anybody to have a surgical abortion, but all of the subjects knew that and signed their informed consent with that full knowledge.

DR. HENDERSON: What kind of risks did you give them if they were to continue the pregnancy after it had failed in medical termination?

DR. ROBBINS: This will be discussed in detail by Dr. Bardin, but I will just say briefly that they have been told that there are risks to them if they continue their pregnancy in terms of possible effects to the developing fetus. So, they were informed of this. These types of warnings are also included in our labeling and Dr. Bardin will speak to some of those when he gives his presentation on safety.

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DR. HENDERSON: I assume when women came to have medical abortions in your programs, you were set up to provide them with surgical abortions. Were you ever faced, I would imagine would happen in your life, with patients, who had no medical coverage and would have to have a surgical abortion? How do you work that into your fees?

DR. ROBBINS: You are anticipating some of the things that will come up during the presentations of the next two speakers actually. Dr. Winikoff and Dr. Newhall will talk a little bit about how this worked in the U.S. clinics.

If you don't mind, I will let them give you some of their first hand information on that.

DR. DAVIDSON: Dr. O'Sullivan?

DR. O'SULLIVAN: I have two questions.

What evidence did you present to them regarding the possibility that something would happen to their fetus? That is my first question.

My second question relates to why the final U.S. data wasn't obtained before this meeting.

DR. ROBBINS: Again, I will allow Dr. Bardin to discuss some of the information that we know about the effects to the fetus.

Go ahead, Wayne. And then I will answer the

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cond question.

DR. BARDIN: As part of the beginning evaluation of the drug, there is an extensive toxicology that is done on the drug, including a section called teratology.

DR. DAVIDSON: Pardon me. Is this going to be part of your formal presentation at this time?

DR. BARDIN: Not in the detail that I think it is being asked now. So, therefore, I thought it appropriate, Mr. Chairman, if you don't mind, I will answer it now.

DR. DAVIDSON: Sure.

DR. BARDIN: Because I don't have a lot of slides on it. I just was saying that there wasn't --

So, in the -- we have animal toxicology on both of the drugs. In some of the animal toxicology on both drugs, there is evidence for teratologic changes in animals. There have been 21 children born to women who changed their mind and there have been three congenital anomalies.

Now, statistically, that is not enough to determine what the effect is in humans. So, not knowing the effect in humans, we advised women about what the animal data showed and said that there was a considerable risk to them if they changed their mind because usually teratologic effects in animals will translate or have a gh possibility of translating to teratologic effects in

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humans.

So, these were the data that were presented to the women.

DR. O'SULLIVAN: And the three congenital anomalies?

DR. BARDIN: Beg your pardon?

DR. O'SULLIVAN: The three congenital anomalies were what?

DR. BARDIN: Three congenital anomalies in the children that were born were a club foot, some abnormal fingernails, and an immune disease which led to death.

DR. O'SULLIVAN: Long-term outcome of the remaining --

DR. BARDIN: The others are normal.

DR. O'SULLIVAN: Normal developmentally?

DR. BARDIN: We have that as of now they are normal. That is all I can tell you.

DR. O'SULLIVAN: One more question regarding -- toxicology. Is animal toxicology always found or always translated into human toxicology or teratology?

DR. BARDIN: Well, what you look for is a chemical reaction in the fetus that will lead to a marked abnormality of a developing organ. One has to be very concerned that if you can demonstrate this in two animal species, that this would translate into a third species.

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So, I think --

DR. O'SULLIVAN: Has any primate work been done to show this?

DR. BARDIN: No. I think one does not normally do teratology studies in primates. That would be extraordinarily expensive and many people would view that to be not possible. We wouldn't get many drugs approved if that were required. So, we use two species and that is done with virtually all drugs that come before the FDA.

DR. DAVIDSON: Dr. Azziz.

DR. AZZIZ: Question for Dr. Spitz.

DR. DAVIDSON: Wait a minute. Was there a second question?

DR. O'SULLIVAN: My second question was related to why this data is being presented without the finalized U.S. data?

DR. BARDIN: If you noted the time line on Dr. Robbins' slides where she had the two arrows, the red and the blue arrows, we began everything in 1994. The U.S. clinical trial began at that time. Preparation of the NDA began with the data from the two pivotal studies. The U.S. clinical trial was completed and as you heard, the sites have just been verified and now, very soon, the analysis can begin. In other words, one has to audit all the sites, all the data, all the case report forms, verify that, lock

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the data and then do the analysis.

That process is ongoing, but in the meantime running simultaneously on Dr. Robbins' two arrows, an NDA plication was completed and submitted to the agency for consideration.

DR. O'SULLIVAN: I understand that. I do really understand how long it takes to collect the data and do the quality assurance, but I still don't know why this meeting is held at this time when the data is not finalized.

DR. BARDIN: Well, because we have sufficient data to -- we have two -- we have sufficient data according --

DR. O'SULLIVAN: From the non-U.S. data.

DR. BARDIN: From the non-U.S. data, to allow us to submit an application to the FDA and with the understanding that the U.S. clinical trial would be done and would be -- as soon as it was completed, the data was locked and it is all written up, it will be submitted to the FDA for their consideration.

And that is just as the Commissioner outlined. So, we are following exactly as he said.

DR. DAVIDSON: Dr. Rarick from the FDA.

DR. RARICK: I would point out to the Committee also that we have this meeting during the review process because, as Dr. Kessler noted, our goal is to take an

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tion on a new drug application that is submitted within six months and we would like your comments and discussion prior to that time line.

DR. DAVIDSON: Dr. Kessler.

DR. KESSLER: You should also know that FDA has insisted that not only the foreign data be presented, but the preliminary safety data that is available to date to be presented to this committee.

DR. DAVIDSON: Any further questions, Dr. O'Sullivan?

DR. O'SULLIVAN: No. I will do it later.

DR. DAVIDSON: Dr. Azziz.

DR. AZZIZ: A question for Dr. Spitz.

The regimen proposed, obviously, has two drugs. The success of mifepristone alone is 80 percent. It increases to 95 percent from the data you presented with the use of prostaglandin. How many patients need misoprostol in these studies? I mean, I assume not all of them went on to use the second drug.

DR. SPITZ: Yes, that is quite correct. The protocol called for the administration, as you mentioned, of misoprostol after 48 hours, but it turns out in this cohort of 2,480 subjects, there were 3.2 percent of women, who, in fact, had a -- whom the commission believed had a plete termination of pregnancy by the time they came to

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the second visit and as a consequence, were not administered misoprostol.

DR. DAVIDSON: One question about timing.

The NDA indicates and requests the second dose at -- the misoprostol dose at 48 hours. Much of the clinical work and in your discussion, you have a window of 36 to 48 hours for that prostaglandin dose. Why isn't that specified in this application?

DR. SPITZ: In fact, basically what happens is the women get mifepristone on the first day and they come back on the third day for the misoprostol. In fact, as I did mention, the maximum sensitivity of the uterus to prostaglandins, there is certainly a window from about 36 to 48 hours. That is why we have really not specified, as long as it is specifically mentions 48 hours later on the third day they come back for the misoprostol.

DR. DAVIDSON: So, you do not advise the misoprostol being given beyond 48 hours?

DR. SPITZ: We have not studied this in detail, but, in fact, from a lot of the other reports in the literature, the best time, the best responses occur between 36 and 48 hours. After 48 hours, there is a slight fall off, not to a very great extent, but when it goes a lot beyond 48 hours, three, four, five days, then the response wears off. Correct.

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DR. DAVIDSON: So, you do not advise the drug being given after 48 hours?

DR. SPITZ: No, we do not.

DR. DAVIDSON: Dr. Lewis.

DR. LEWIS: I have a question about the cardiovascular events seen with sulprostone.

DR. SPITZ: Yes.

DR. LEWIS: Did that cause any change in the qualifications of women for this protocol? Was there any predisposing factor among those women who had the cardiovascular events that led to your --

DR. SPITZ: I would just like to, you know, put on record that cardiovascular events, none have been reported with the present regimen under discussion with mifepristone and misoprostol. None have been reported and also there have been no cardiovascular reports with the other prostaglandin, gemeprost. There were only, as I mentioned, these cardiovascular effects, which occurred with sulprostone, which was given parenterally and it is believed that probably some of it got in intravenously and it is also another type of prostaglandin. And it occurs in 1 in 20,000 women. There were three cases of hypotension, one case of a myocardial infarct in the formal publication and from a review of the whole literature, there have been another two patients with myocardial infarctions, only one

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of which was fatal.

So, although in the clinical studies, we have really taken cognizance really not to enroll women with -- the pivotal studies -- the exclusion criteria really was if they had cardiovascular risk factors, they were really not included, but basically we do not believe that, in general, clinical practices would apply because no cardiovascular effects have been seen with any of these other prostaglandins, other than the parenterally-administered PGE2, sulprostone.

DR. DAVIDSON: Any other questions from the Committee?

Dr. Daling.

DR. DALING: In talking about the women, you had 21 women, who did not complete the regimen. What was the denominator for that figure? How many women were involved in that trial that resulted in 21 women changing their mind?

DR. BARDIN: The 21 women that changed their mind, they weren't all in the clinical studies. A lot of those were in general use.

DR. DALING: So, you don't have any figure on how many women changed their mind?

DR. BARDIN: In the clinical trials?

DR. SPITZ: Yes. In the French pivotal study, we

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In these -- yes, we had -- in fact there were 13 women -- never received misoprostol, 13 women. They only received the mifepristone because some of them didn't wish to have the misoprostol. They actually had termination of pregnancy. Out of this 2,480, there were 13, who did elect to go on to misoprostol.

DR. DAVIDSON: One other -- Dr. Petitti?

DR. PETITTI: In your efficacy data, you have a model, where you used various factors to predict efficacy. Was there any relationship at all, not just a statistically significant relationship between body mass index and effectiveness?

DR. SPITZ: Yes. In fact, that is an interesting question because this has been reported with the use of misoprostol, when it was given -- mifepristone alone. And, in fact, in a very careful analysis, we did not find that this body mass index had any effect whatsoever in the pivotal studies -- in these pivotal studies on the efficacy. There was some minor relationship possible with the rate of expulsion, but this was really not consistent. So, we could not find this at all.

DR. PETITTI: Was it a positive or a negative relationship, higher rates of expulsion with higher body mass index or the opposite?

DR. SPITZ: That is what it seemed to indicate.

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That is correct, that the higher the weight, the earlier the expulsion, but this was really not consistently seen right through. That is why I elected not to mention it, because this is a minor -- it is of borderline significance.

DR. PETITTI: Thank you.

DR. DAVIDSON: A routine clinical use question.

In the review of your clinical data --

DR. SPITZ: If we could have that light off -- it is just very hard. I mean, I can't see anything.

Thank you.

DR. DAVIDSON: You have probably interfered with technology at a level that will not easily be excusable.

DR. SPITZ: Well, look, I gave you my qualifications.

DR. DAVIDSON: But I haven't forgotten my question.

In your clinical data -- I mean, in your research data, you excluded women with alcohol or tobacco use and also over 35. Each one of these would be practical issues in the American experience for the use of -- why were those exclusions made and what would be the advice for people who drink moderately or smoke?

DR. SPITZ: In fact, in the French pivotal -- the first pivotal French study was -- the exclusion criteria

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was anyone over the age of 35. But, in fact, in the second study, there was no exclusion criteria and, in fact, 150 women were actually over the age of 35 in this. The only exclusion was if they were over the age of 35 and they smoked. This is really anecdotal. This really comes from that subject with the coronary -- with the problems with the myocardial infarction, the hypotension, where it was believed that cardiovascular risk factors might be important.

But, you know, we do not -- we have not listed that as an exclusion criteria for clinical use of this compound.

DR. DAVIDSON: Are there any further questions?

[No response.]

Okay. You may proceed with the rest of your formal presentation.

DR. BARDIN: Thank you.

My name is Dr. Bardin and I am going to review the safety of mifepristone plus misoprostol. And I think a number of the questions that have been asked will be -- maybe will move toward a better resolution as we look at these data.

I would like to begin by reviewing the rationale for reporting the adverse events for the combination of mifepristone and misoprostol, the two drugs together,

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rather than separately in this presentation.

First, as you have heard, there is evidence for synergy between mifepristone and misoprostol; that is, the .tion of these drugs together is greater than additive. So, they are viewed then as sort of one regimen.

Secondly, women come in with lots of symptoms of pregnancy, nausea, vomiting, cramps, and then the drugs that are given increase many of these symptoms. So, we are talking about a regimen on a regimen of pregnancy.

Then, finally, there are no multicentered studies of oral misoprostol alone during a pregnancy at the dose we are recommending here.

How are these side effects or adverse events, as I am going to call them, collected? Well, at each visit, a form was filled out that in the first visit recorded the symptoms of pregnancy, in visit two, all the adverse events that had occurred since the first visit, and then there was a focus on this short four to five hour observation period after the prostaglandin, where adverse events were recorded and then there was visit three, where all the events since visit two were recorded.

Then any other emergency room visit, any other visit to the doctor for any sorts of problems, that those events were included and some patients were even followed out as long as 70 days to evaluate bleeding in women who

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d had a successful abortion. All these were put together d each woman was asked to classify each adverse event as minor, moderate or severe.

Throughout this presentation, I will be referring to severe events. The two ways we think of severe events are shown on the next slide. First, there is the severe events as judged by the women themselves. These are the most common events that were seen in the clinical trial, bleeding, uterine contractions, nausea and vomiting, all predicted outcomes of the mifepristone and the misoprostol.

So, the women decided what percentage of these were severe. But we will also be referring to another kind of severe event and these are severe as judged by medical outcome. And these would be a severe cardiovascular event, any hospitalization, a surgery that was required, say, for bleeding or a blood transfusion.

I will try to distinguish which of the two kinds of severe I am talking about, as we proceed through this.

The next slide shows sort of the good news, the overview of what I am going to talk about. The animal studies show that there were no toxic effects in animals that would be reflected in the women. In humans, there were no deaths or no serious cardiovascular outcomes in any of the two pivotal studies. In humans, there were no pected adverse events. Virtually, all the adverse events

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were related to the pharmacologic actions of the regimen and, indeed, some of these are essential for efficacy, such as cramping and bleeding.

The next slide shows the average number of adverse events in three different groups of women that were distinguished by the number of doses of misoprostol that they received. As you have just heard, there is a small group of subjects that have their abortion prior to the second visit. So, they receive no misoprostol. And in these individuals, shown by the red bar, they have less than one adverse event per patient.

By contrast, if you add one dose of misoprostol, the number of adverse events per patient rises to two and a second dose of misoprostol, the average adverse events per patient rises to three. As you have heard from Dr. Spitz, two doses of misoprostol do not improve efficacy. So, since there is an increase in number of adverse events in this group, we would certainly not recommend that a second dose of prostaglandin be given. And, certainly, this has been dropped from the U.S. clinical trial and it is not recommended in our labeling.

Now, what percentage of patients actually complain of one or more adverse events? Well, this is shown here with percent of patients that complain of adverse events. Here are the three groups that I have

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shown you from the previous slide. So, we see that in women who receive no misoprostol, 18 percent of them complained of one or more adverse events.

By contrast, a single dose of misoprostol increases the percentage of women that complain of one or more events to 90 and a second dose of misoprostol increases the percentage to 96. Above each bar are the number of women in each of these three groups.

The blue portion of each bar represents the proportion of each group that indicated that their adverse events were severe, so that you can see that in each of the three groups, there were somewhere between 20 and 30 percent of the adverse events were judged by the women themselves to be severe.

Now, the next point is when do the majority of adverse events occur. Here we have the total adverse events shown on this ordinate on the left and on the right ordinate, we show the adverse events expressed as a percent. So that a 100 percent is equal to the total. If you look at the number of adverse events that occur immediately after the misoprostol, during the visit to the clinic in visit two, you see that 65 percent of all the adverse events that were reported were observed at that period of time.

The blue portion of each bar, as on the previous

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slide, represents the proportion of the adverse events that were judged to be severe by the women themselves.

This slide puts into perspective what I have just shown you on the last slide; that is, here we have the entire time frame of observation for adverse events and there is a four to five hour period on the third day during which 65 percent of the adverse events were reported. This tells you several things, but most importantly it says that most of the adverse events were of short duration. And, in fact, except for bleeding, which can occur over several days, most events that were judged to be adverse occurred over a very short time frame.

The next slide shows you what the adverse events actually are. Here we see the percentage of women that complained of each of the adverse events that are shown here. The blue bar shows you that the most commonly recorded adverse event were painful uterine contractions occurring in 82 percent and the red bar shows you the combined GI complaints, including nausea in 45 percent, vomiting in 20 percent and diarrhea in 15 percent.

The orange bars that you can just barely see here are the next most common group of events occurring in 1 to 3 percent; headaches, 3 percent; fainting, dizziness and metrorrhagia or increased bleeding, 2 percent; anemia, asthenia and chills and fever in 1 percent.

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Note here the metrorrhagia or the increased bleeding and the anemia. We will return to these when we talk a little bit more about bleeding in general. But these -- when you ask about what women think are the adverse events, these turn out to be 2 and 1 percent, even though as you will see, almost all women bleed.

Now, in order to show you the adverse events that occur below 1 percent, which I am going to do now, we have to expand this part of the scale down here so you can even see it, and that is shown on this slide, where now the top part of the scale, rather than being a hundred percent, is 1 percent. This is the incidence of adverse events with 1 percent at the top of the scale.

So you see that hot flashes occur in slightly more than half a percent, then skin conditions, anxiety, all breast conditions, including discharge, pain, itching and everything are less than half of a percent; palpitations -- this represent five subjects -- so, you see we are getting down to small groups -- tachycardia, five subjects, and toothache is out on the far end of the scale.

There were a total of 77 different kinds of adverse events reported. I have shown you 18 of those and they are the most common. So, all the rest of the adverse events occurred in something less than five patients, usually one or two subjects only.

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So, I have shown you the most common adverse events, but let's now go back and look at the most common and ask how serious were they as judged by a variety of criteria.

On the next slide, we look at painful uterine contractions. For these three bars on this scale right here is percent of patients and the top of each bar is a hundred percent. So, if you look at the central bar here of above painful uterine contractions, the 100 percent here is the total women in the study. So, 82 percent of these women, shown by the green part of the bar, experience painful uterine contractions, as I have shown you from a previous slide.

Now, of this 82 percent, what portion were really judged to be severe by the women? Well, if we set that 82 percent to a hundred percent, as shown by this bar on the left and then say what are severe, then the blue portion of this bar say that 32 percent of women that had uterine contractions said they were severe.

That is one measure of how many could have been severe. Another measure would be how many needed treatment of some kind. So, if you say what percentage of 82 percent needed treatment, if you set that to a hundred percent again, as we have done on the right, and now look at that bar, 20 percent, as indicated by the yellow portion of the

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bar, needed treatment.

What treatments did this 20 percent get? That is shown on this yellow bar on the far right. Now, the percentage here refers to the percentage of this 20 percent and you can see that 55 percent got antispasmodics, 31 percent, narcotics, 11 percent, non-narcotics and 3 percent all others.

People have said, okay, you have 31 percent here. Does that mean 31 percent of the women got narcotics? The answer to that is "no." It is 31 percent of 20 percent and 20 percent of 81 percent and if you quickly figure that out, that means that 5 percent of all women in the study received a narcotic for a painful uterine contraction.

So, this is the kind of analysis that we have done on each one of these to figure out what percentage of the women were actually treated and with what for their treatment.

On the next slide I will show you a similar but not so complex analysis of the GI conditions. This is the percentage of all GI conditions reported by women that might have reported one or more conditions, which would include nausea, vomiting or diarrhea.

Regardless of which one of these conditions were reported by the women, about 20 percent of women under each of these categories said that this was a severe adverse

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event. However, only 4 percent of the women who had GI conditions of any type requested or received some type of medication for that event.

The next slide returns to bleeding. This reviews something that may be obvious to many of you. First, that any patient that is going to have a successful outcome with this medication is going to bleed. So, most of the women that got the medication, 96.6 bled; 33 percent bled prior to misoprostol. The mean duration of bleeding was 9.1 days and the longest duration was 69 days, with the next most lengthy, 45 days and rapidly falling off after that.

This wasn't bleeding. This was spotting and this was a women who had had a successful abortion. But it gives you an upper limit of what could occur.

Now, this doesn't tell you anything about severity. The next slide shows you severity of bleeding as judged by four separate criteria.

The first criteria, the women, while they were in the clinic, did they get any medication that could have been used to treat bleeding, saline or something that contracts the blood vessels? That kind of medication was given to 13 percent of the women. This is the upper part of the scale, this 15 percent, percent of patients who had one of these events.

Drug treatment, 13 percent. This shows the

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rcentage of women that had a decline in hemoglobin of greater than 20 percent by the third visit. This is 3 percent. I have already told you that 2 percent of women complained of metrorrhagia. Virtually all women bled.

The women that bled said that their bleeding in 80 percent of the time was heavier than their heaviest menstrual period, but only 2 percent of those women said that it was truly severe or excessive; therefore, we classified it as metrorrhagia or severe bleeding as judged by the individual.

1.4 percent of individuals had a bleeding event, which could be termed severe, based on medical outcome and that is shown on this slide. This is treatments for medically severe bleeding, as judged by the fact that a woman went to the hospital. That was 21 women out of 2,480. Two received a surgical intervention to stop bleeding and there were four transfusions.

Now, in the studies that you have heard about in the past, there has been great concern about cardiovascular events. So, one of the purposes of this clinical study, these two pivotal trials, was to carefully look at cardiovascular events after the prostaglandin. So, every individual that received prostaglandin had blood pressure measured and here are three measures of that examination at occurred in the clinic.

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When all patients have their blood measured and you say how many patients had a decline in blood pressure of greater than 20 percent, either systolic or diastolic, it is 420. That is 17 percent of women. However, when you ask of that 17 percent how many really had what you would call clinically significant low blood pressure or clinically significant hypertension, that is only seven women in this study and only one of those was judged to be severe.

Interestingly, there was an increase in blood pressure of greater than 20 percent and almost an equal number, 16 percent, and 8 percent of women still had hypertension when they were discharged from the clinic.

Tachycardia, as I have said, was in five; one of those was severe, and even those with these who were judged to be severe, there was not a lasting serious outcome from either of these individuals.

I would now like to turn to a comparison of the severe adverse events reported to the FDA in the U.S. clinical trials, which are shown here. These are the events. These are the numbers of patients and the percentage of women out of the study that had those events and they are compared in the right hand column with similar events from the French study.

So that 1 percent of the women in both trials had

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hospitalizations. Far less than 1 percent had transfusion. That is one-sixth of 1 percent and one-fifth of 1 percent in these calculations. Two percent had severe hemorrhage in both studies. Two percent of women in the United States had a surgical intervention and 1 percent in France.

So, these data look like that these studies are certainly similar.

In conclusion, the risk of adverse events has been determined in two pivotal studies. As a result, labeling has been written that informs women about the risk of this regimen.

The most frequent adverse events, painful uterine contractions and GI symptoms, were expected outcomes of the regimen. Sixty-five percent of events were immediately after the misoprostol at the time of the second visit. Eighty percent of women required no pain medication whatsoever to use this regimen.

Bleeding occurred in all women with a successful outcome. Rarely, excessive bleeding requiring hospitalization or transfusion or curettage occurred. Cardiovascular events, including clinical hypertension, hypotension and tachycardia were rare. Only two were considered severe and these were resolved without long term consequences.

So, I have reviewed for you the general data that

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suggests to the clinicians and to the scientists that have evaluated these data that this drug regimen can be judged to be safe, as well as effective.

DR. DAVIDSON: Would you stay there just for one moment, please.

Dr. Barick, would you explain to the Committee, since this word is being used often, what "pivotal" means?

DR. BARICK: I don't think "pivotal" has a regulatory definition. "Pivotal" is simply a term that is constantly thrown around as the large, well-controlled trials upon which the safety and effectiveness information is being based. The termination of "pivotal" does not have any standard definition. It is something that can be used by the sponsor or we, but it is not a regulatory defined term.

DR. DAVIDSON: Okay.

Any other questions?

DR. HENDERSON: For the treatment of symptoms, what antispasmodics were used? --

DR. BARDIN: Many different ones. I can give you the list. We have them listed in the NDA, all the kinds that were used.

DR. HENDERSON: For example?

DR. BARDIN: I will have to get the list.

DR. DAVIDSON: Dr. Azziz.

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DR. AZZIZ: You had a few patients, Dr. Bardin, that required surgery for excessive bleeding, most of those, I assume, are curettage, all of them. Were there other surgical interventions required?

DR. BARDIN: The surgical interventions actually defines the -- those were the -- yes, the answer to your question is those were the only kinds of surgical interventions and the surgical intervention is really how we define failure. Dr. Spitz showed the three categories of women that had a surgical intervention, those that had a continuing pregnancy, those that needed one for bleeding, which have been repeated up here, and those that were needed to remove products of conception that were not passed.

DR. AZZIZ: In your study, none of the women then required a hysterectomy for control of bleeding?

DR. BARDIN: No.

DR. DAVIDSON: Do you have any vomiting -- and even severe vomiting occurred in about 20 to 25 percent of the cases. Can you comment on whether or not vomiting occurred early enough after the misoprostol that you thought it interfered with absorption? Or can you comment about that relationship between drug effectiveness and vomiting?

DR. BARDIN: Thank you for that question. It is

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very important. I am happy that you brought that up.

The way misoprostol is formulated, if you have ever touched it when your finger is wet, literally before you can get it off the end of your finger or just as soon as you can swallow it, the pill dissolves and there is very rapid absorption. Most of the symptoms arose slowly and peaked sort of around one hour and it is in accordance with the blood levels of the prostaglandin.

So, it is the prostaglandin that brings on these symptoms, as I have suggested by the slide in which almost all of the side effects occurred at the observation period and the ones that occurred by far and away the most frequently were contractions of the uterus and of the GI tract.

DR. DAVIDSON: So, in that regard, patients did not require a second dose of the prostaglandin due to --

DR. BARDIN: Almost never.

DR. PETITTI: I imagine that you have looked at your data in many ways and perhaps you have looked at this way. I would be interested in the percentage of all patients, who had at least one severe GI symptom, where the denominator is everyone who walked in the door and the numerator is severe symptom of either nausea, vomiting or diarrhea, if you have that.

DR. BARDIN: I do have that and I neglected to

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make a slide of it. I don't recall it because it is --

DR. PETITTI: Perhaps you can --

DR. BARDIN: I did the same kind of analysis that I did for the painful uterine contractions, but I didn't think I could get away with showing that kind of complex slide too often.

DR. PETITTI: Well, perhaps you could --

DR. BARDIN: I will be happy to share that with you. It is written up, yes. It is actually -- it is written up in that way in the report to the FDA. So, I will share that for you. I will look it up.

DR. DAVIDSON: Dr. O'Sullivan.

DR. O'SULLIVAN: Can I just make sure I understand this. The data that you just presented is the European data. It is not the U.S. data.

DR. BARDIN: I did present the --

DR. O'SULLIVAN: The medical situation you presented was the U.S., but the side effect data of the patient --

DR. BARDIN: Yes. The patient assessment of what the patient told the doctor when they said, you know, what have you --

DR. O'SULLIVAN: That is all European.

DR. BARDIN: That is all European. That is right.

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DR. O'SULLIVAN: So, we don't have any of the American as yet.

DR. BARDIN: Not yet. That will be available round the end of the year.

DR. KOSASA: What was the oldest patient that received this medication?

DR. BARDIN: Do you remember the oldest patient?

SPONSOR: 46 --

DR. BARDIN: We will look that up. We will tell you in just a minute.

DR. KOSASA: And then you don't have an indication for age on your application, so we can go up -- there is no age limit?

DR. BARDIN: No, there is not an age limit. There wasn't an age limit in the second trial and we have patients above 35 days -- 35 years. So, we have no firm date of when there should be a cutoff. We know that the prostaglandin has been used across all age groups.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: You obtained CBCs on all of the women who enrolled in the trial before they received the medication. Correct?

DR. BARDIN: Yes.

DR. HENDERSON: Is that part of your labeling? Are you going to suggest that all women have a CBC, a

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recent CBC before they receive the medication?

DR. BARDIN: I don't think that is a requirement of the labeling. I think that every physician who cares for an individual -- the labeling says something, you should do all of the things that are required for good obstetrical practice and we focused particularly on things like RH immunizations and the precaution that one needs to take there or the precaution that one needs to take if there has been a previous endocarditis.

Then we say that any other thing that needs to be done consistent with good obstetrical practice, and, so, we didn't say get a white count, get a red count, but I think that would be included under good practice.

DR. HENDERSON: I ask only because of the incidence of anemia that you listed and if that is a concern, then might not one want to make sure that women are not anemic before they receive the medication?

DR. BARDIN: I think it is always a concern and that is -- and the percent of anemia was really judged as a fall in hemoglobin of greater than 3 grams. I think the lowest patient in the study was 10 grams, if I remember correctly. So, in many women, many women are anemic during pregnancy, but I think we will -- we are going to have a clinician, who has dealt with this talk about this, and she going to address some of these issues of bleeding in her

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presentation. And you will be interested in it, yes.

DR. DAVIDSON: Dr. Kessler.

DR. KESSLER: Dr. Bardin, you presented the serious adverse events in the U.S. clinical trial and you had a slide that compared them to the French. In your further analysis, do you believe that it is likely that those would change or is that, do you think, a relatively complete picture?

DR. BARDIN: I don't believe the transfusions will change. I think we know those. I don't believe the number of hospitalizations will change and I don't believe that any of those numbers are going to change to really make a substantial change in percentage.

DR. KESSLER: You believe that is a complete picture.

DR. BARDIN: I believe that it is certainly close. The numbers -- the number of people in those columns will change, but I do not believe that the percentages of overall women will totally change because I think there can always be a physician who didn't report something that another physician would have said was a severe hemorrhage. The physician says, oh, I see this -- I see worse than this in all the miscarriages I manage. So, they don't judge it to be serious and they don't report it to the FDA.

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We will see this in our reports, but I don't think that is going to change the percentage.

DR. DAVIDSON: Yes, Dr. Harrigan.

MS. HARRIGAN: Could you just recapitulate the comparison of the American and the French data for those four events? I don't think we have that --

DR. BARDIN: If we could show the third from the last slide. So, let's see -- do you still have -- one more forward.

So, here are the serious adverse events as reported to the FDA for the U.S. trial. And here are those -- here is the number of women in the U.S. trial. Here are the number of adverse events -- the number of women who had these serious adverse events. In parentheses are their percentage of this total. And here are the same kinds of comparisons for the French data. This is the total in the French data. These are the number of women who had these adverse events and these are the percentage.

Dr. Kessler's point was to the fact that we know these numbers are absolutely with certainty and they will not change. His question was how many of these numbers do we believe might change. So, to the comparison, it is 1 percent of the patients in each trial had hospitalization. Far less than 1 percent, only 4, and in this trial it takes 24 patients -- as you can see, 24 patients, 24.8 patients

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to make 1 percent. So, this is far less than 1 percent and here is 2 percent and 2 percent for severe hemorrhage or metrorrhagia, as we have called it, as it was called in the French study, and 2 percent with surgical intervention for bleeding and 1 percent in the French study.

DR. DAVIDSON: Dr. O'Sullivan.

DR. O'SULLIVAN: I do have a question.

Let's go back to surgical intervention. What exactly do you mean by "surgical interventions," before I ask my question?

DR. BARDIN: Okay. Can we turn the lights again so we can see the slide?

Okay. This is surgical intervention for bleeding. You recall, on Dr. Spitz's slide, there are three reasons for failure. A failure is when the medical abortion does not occur and a surgical procedure is required. There are three reasons for that.

Number one, if the patient comes in and they are bleeding a lot and the physician or the patient decides that is too much bleeding, a D&C is done.

Secondly, after a certain period of time it is decided that there are still products of conception in the uterus, but there is not a lot of bleeding, the surgery is not for bleeding, it is for just to remove products of conception.

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Third, there is clearly a continuing pregnancy, as defined by ultrasound.

DR. O'SULLIVAN: Okay. But this is clearly for bleeding.

DR. BARDIN: This is clearly for bleeding.

DR. O'SULLIVAN: And by "surgical intervention," are you including aspiration, as well as D&C?

DR. BARDIN: Aspiration and D&C, whatever the physician used.

DR. O'SULLIVAN: It will be interesting to see how the numbers actually play out because not unexpected, in my mind anyway, is the fact that you have more interventions -- sure, it is only 1 to 2 percent, I agree, but that doesn't seem to be a big change, but there certainly is more in the U.S.

DR. BARDIN: Okay. But remember -- you have to remember that this can be either the patient or the physician.

DR. O'SULLIVAN: I understand. Yes.

DR. BARDIN: So --

DR. O'SULLIVAN: That is exactly why I am making the point.

DR. BARDIN: What you are really interested in is of the women who had interventions for bleeding, how many them even had a change in their hematocrit, right?

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DR. O'SULLIVAN: No, no. What I am really interested in is how tolerant the American woman is as contrasted to the European woman for bleeding and how much she is willing to put up with.

DR. BARDIN: That was the flip side of what I was alluding to. I would say --

DR. O'SULLIVAN: The physician's indication for doing it may be altogether different.

DR. BARDIN: We are well aware of that and that is clearly -- you are right on. That is just correct because, clearly, there are some women who said, "I have had enough; I think I will terminate this," and there are some of these and that could be because she is continuing to have bleeding which is the same as a menstrual period. That could be. But you saw that there were some women that had had a successful termination that continued to spot, and they elected not to have a surgical procedure --

DR. O'SULLIVAN: That is the European data.

DR. BARDIN: Okay, but -- well, those data will be available.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: Can you, the best you can -- you have "hemorrhage" on this slide. You used "metrorrhagia" on a previous -- can you give us some sense generally of that definition for these data?

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DR. BARDIN: In the French data, it was, as I pointed out, all women bleed, and then you ask the women what was that bleeding like and 80 to 90 percent over a series of several studies that were done in France said that my bleeding at the time I took this drug regimen was 80 -- 80 to 90 percent of them said the bleeding is heavier than my heaviest menstrual period. Okay?

So, this is a regimen that produces in most women more bleeding than their heaviest menstrual period. But then at the end of the study, all women were asked did you have excessive bleeding, and 2 percent said, yes, I had too much bleeding. That is what the 2 percent in the French study is from. It is from the women's judgment at the end of the study.

So, it allows you to kind of look at this perspective from several points of view. Women are bleeding more than their heaviest menstrual period, but only -- they have to bleed a lot before they will say it is too much.

DR. KESSLER: And the U.S. definition?

DR. BARDIN: The U.S. definition, it will be similar.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: In part of the material sent to us, there was a mention of someone who had meningitis. Do

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you have any details on that?

DR. BARDIN: Meningitis?

DR. RARICK: There was one viral meningitis in e U.S. study.

DR. BARDIN: Oh, is that right?

DR. RARICK: A hospitalized patient.

DR. BARDIN: A hospitalized patient. Okay.

DR. RARICK: Causality has not obviously been determined. There is a couple of those.

In our presentations, we will break down some of these particular events for the U.S. If you don't have that readily available, we will.

DR. BARDIN: I don't think we have it broken down by individual patient.

DR. DAVIDSON: Are there any further questions?

DR. ROBBINS: Just to get back to some data that was asked for, so you can have it right now.

Here is the list of the different types of antispasmodics that we used for the uterine contractions. So, if you want to see that.

DR. BARDIN: It is such a long list. I am not going to -- here they are.

[Dr. Bardin hands Dr. Henderson the list.]

DR. ROBBINS: Here are some numbers in terms of the number of people in terms of nausea for vomiting and

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l the severity here.

DR. BARDIN: I am going to study this and tell it to them. I am not going to try to do it up here.

DR. DAVIDSON: You want to continue with your formal presentation?

DR. BARDIN: Yes. Are we going to have a break?

DR. DAVIDSON: Will it take longer than 10 minutes? It will? Well, let's take a break for 15 minutes.

[Brief recess.]

DR. DAVIDSON: Could we reassemble, please.

Would The Population Council continue with its presentation, please.

DR. WINIKOFF: Good morning. Yeah, it's still morning? My name is Beverly Winikoff. I am from The Population Council. I am a public health physician and program director for reproductive health at The Population Council.

This morning I would like to address the issue of the acceptability of mifepristone/misoprostol for medical abortion to women and to the providers of health care for women.

Unwanted pregnancy is a serious and stressful problem for women. Safe, effective, and humane remedies for this problem have been sought since earliest human

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1 history. Medical abortion represents a new advance in the
2 ability to offer women options for solution of this
3 problem.
4 It is important for us to know whether this is an
5 option that women feel they would like and whether the
6 providers of health care for women will find it a
7 reasonable and feasible option to offer women.
8 Medical abortion was originally developed outside
9 of this country, as you've heard. Since it was originally
10 offered outside of this country, the first assessments of
11 its acceptability to women involved patients from other
12 countries.
13 The published literature shows 12 reports about
14 the reactions of women to early medical abortion. These
15 reports were done in six countries, all on experimental
16 regimens, virtually all, and all on small groups of women.
17 Yet despite the scattered nature of this
18 literature, the findings of these reports are consistent
19 and strongly support a very high preference of women for
20 medical methods of terminating pregnancy.
21 In general, these reports suggest the following
22 reactions of women: medical abortion seems to be the
23 preferred option as a choice over surgery in about 60
24 percent or slightly more of women in most studies.
25 There are very high levels of satisfaction with

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1 medical abortion procedures recorded in all studies, and
2 women express a great willingness to use the method again
3 and to recommend it to others.
4 I would like to focus specifically now on the
5 acceptability of mifepristone/misoprostol for early medical
6 abortion in the United States. We are just beginning to
7 see how American women react to this new type of therapy,
8 and for our conclusions, we have looked to the U.S.
9 clinical trial, interviews with patients from that trial,
10 and focus groups of providers who participated in the
11 trial.
12 We have seen through all of this information four
13 very strong trends: one, women in the United States like
14 this method overwhelmingly. For them and their providers,
15 it is a very different therapy from the alternatives
16 available to them.
17 Third, U.S. women seem not to differ in their
18 reactions to this medication from women in other places.
19 And, fourth, U.S. providers want to offer this option to
20 women.
21 The first source of information that we have
22 about the acceptability of mifepristone/misoprostol to U.S.
23 patients come from The Population Council's U.S. clinical
24 trial and includes almost 800 women seeking abortion who
25 are 49 days or less since their last menstrual period.

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hese women were all study volunteers in the 17 articipating clinics in 15 states.

Approximately one third of these women came from cial or ethnic minorities. We don't have exact numbers n these data, since the data are preliminary and may hange slightly. But we have very close to clear references here.

The following questions were asked. These were ll asked at the final visit to assess acceptability to the atients. Patients were asked if the experience was what hey expected it to be, how it compared to any previous xperiences they had with abortion, if they would use the ethod again, and if they would recommend it to others.

Half of the patients thought the experience was ust what they had believed would happen. One third of the atients said that their experience was actually better han what they had thought would happen, and one in eight hought that the experience was worse than what they had nticipated.

We asked specifically about issues relating to leeding, pain, and the place where the abortion took lace. All of these issues have been cited as potentially roblematic for patients, and we wanted specifically to ow more about them.

With respect to bleeding, which was in almost all

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ses not clinically problematic, the single most common nswers were that both the length and amount of bleeding ere as expected.

The next most common answers were that bleeding nd pain were longer and more than had been expected. Not urprisingly, women for whom the method failed to work ended to report more and longer bleeding than women for hom the method did work.

We asked patients how painful the experience had een relative to expectations. More than half of the women eported the experience to be less painful than they had xpected, and the next most common response was that the xperience was as expected.

We asked women, also, if there was a problem with he time or place at which the abortion took place. Less han one in 25 patients indicated that there was any type f problem with either timing or place of abortion.

Women were asked to rate how satisfactory the ntire procedure was for them overall. More than nine in en of the women were very satisfied or satisfied with the xperience, and fewer than three in 100 were unsatisfied.

Half of these unsatisfied women had experienced reatment failure. Even among the women for whom the ethod did not succeed overall, however, two thirds pressed that they were very satisfied or satisfied with

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1 the procedure.
2 Women were asked to predict if they would choose
3 this method again, and more than nine in ten said yes, they
4 would choose this method of abortion again. More than
5 three quarters of the women for whom the method did not
6 work also said they would try the method again.
7 For women who could make the comparison, we asked
8 how this method compared to their previous experience.
9 More than nine in ten of such women rated medical abortion
10 as more satisfactory than surgical abortion. Even two
11 thirds of these women who had experienced failure said the
12 medical abortion was a more satisfactory method for them.
13 Finally, we asked women if they would recommend
14 this method to a friend or relative. Almost everyone in
15 the study said yes, they would recommend this method,
16 including more than four of five of those women for whom it
17 did not work.
18 Since the United States has a diverse population,
19 we wondered if different kinds of women would have
20 different reactions to medical abortion. But there were no
21 differences by race or ethnicity or method of payment in
22 response to questions about satisfaction and reactions to
23 other methods of medical abortion.
24 We plan to do more extensive analysis on these
25 issues in the future. But we have also had a chance to

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1 learn something about why patients may have valued the
2 medical abortion experience so highly.
3 These are the reasons that emerge most commonly.
4 Women are particularly enthusiastic about the ability to
5 avoid surgery and anesthesia. They mention that the
6 experience is more natural in their minds than a surgical
7 abortion, and they value this.
8 Women who choose this method often comment on the
9 sense of control or autonomy that it gives them, and they
10 value this as compared to surgery. These themes were
11 expressed by women interviewed in one of the clinics:
12 "I didn't like the idea of a surgical abortion,"
13 said one. "I don't like any type of surgery at all," said
14 another. "I don't like anything that involves anesthesia."
15 Many women compare their experience with medical
16 abortion to a miscarriage. "I've had a miscarriage before.
17 It's just like having a miscarriage."
18 Some compare it to other commonly known and
19 natural events. "It felt like my period, so it felt like a
20 natural process."
21 Women clearly value the control and autonomy
22 offered by the method. "It offers a lot more control,"
23 said one explicitly. "Your body does it itself," said
24 another. "This was more my body discharging it than
25 someone going in."

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Patients clearly like this method, and it appears that American providers do, too. According to a survey conducted by the Kaiser Family Foundation, currently only percent of all U.S. OB-GYNs provide abortion services. Yet when these providers were asked if they would provide mifepristone/misoprostol were it available, the survey predicted a 66 percent increase in the number of OB-GYNs who were offer medical abortion if it were available.

There are logistical issues with this therapy that have made some providers wonder whether they would indeed like the method. Among these issues are the fact that the counseling involved can be time-consuming; that there may need to be extra time given in speaking to patients; that providers may find it difficult to wait for the results of medical abortion when they are used to a quicker surgical procedure; that patients and providers are not used to observing the bleeding that is involved in an abortion where surgical abortion extracts the blood quickly in one procedure, but in medical abortion the blood comes out over time.

Also, some providers are worried about the logistics of serving medical and surgical abortion patients simultaneously, fearing that it could overwhelm the services that they have, and they also may fear that they need extra space and extra bathrooms, which could be

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oblematic.

We wanted to assess whether these issues in practice would indeed create obstacles to provider enthusiasm for the method. So we interviewed all the providers who offered medical abortion in the U.S. clinical trials. To do this we conducted focus groups in each clinic. We interviewed 78 providers of all types, including physicians and nurses and other kinds of clinicians such as midwives or nurse practitioners.

We also interviewed all of the counselors and administrators who had to deal with the drug. We interviewed people in all 17 clinics in the 15 states.

Four outstanding attitudes were apparent at all sites. One, providers want to offer this method to women, and indeed, in all the clinics, we were told that they would like to be able to offer this method on a continuing basis.

Providers think women like this method very much. Providers feel that they get better at giving this method to women with some practice. And providers become even more positive in their attitudes toward the method with some experience with it.

I want to share with you some of the things that providers said. It was clear that providers were enthusiastic about being able to offer a choice to women.

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"I desperately want it here," said one doctor. "I would offer the option." "I had spent the previous 22 years working for an abortion clinic doing surgical abortions and listened to women ask, 'Isn't there some other way?'"

Providers were particularly interested in providing this method in part because they perceived it as being so well received by women. Most providers felt that women preferred medical abortion in general. Some providers said things such as, "Even the ones that failed, and even the ones that I thought had a terrible experience in terms of the physical symptoms, for the most part said, 'I would do it again. I like this method.'"

Interestingly, even with the relatively few patients that each provider was able to see during the clinical trial, the providers felt strongly that they got better at providing this method with practice. The learning curve just in dealing with this from the clinic's point of view and from the doctor's point of view. "I learned a lot," said one.

A health worker said, "We weren't very efficient at the beginning. At the end it was beautiful because we'd hardly done as well at the beginning as we did at the end."

Providers also liked the fact that they could use the women's waiting time in the clinic for counseling about pregnancy prevention in the future.

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Not only did providers feel that they got better at offering the method; they also seemed to feel more comfortable with the method and actually liked it better as they gained experience with it. "I really didn't expect to like this," said one doctor. "I thought it would be very time-consuming, and I was really amazed at how easy it was and how much women liked it."

Another doctor said, "Most of us said we'd never do it. And then I realized, no, I'd take mifepristone. I'd rather do it instead of taking my chances with who knows who out there for a surgical procedure."

These first experiences with mifepristone/misoprostol suggest that it will be well received and well managed by American physicians. We need to realize, however, as we go forward that the system of distribution of this drug in Europe, where it's now used, is quite different from our usual distribution mechanism for pharmaceuticals in the United States.

As a result, we intend to begin distribution of this drug quite cautiously in a mode similar to the way that international experience with this drug has occurred so far.

Because this therapy will be new for American physicians, there will be extensive provider education in how to provide this treatment to patients.

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Mifepristone will be supplied directly to providers by the distributors, and it will not be sold in pharmacies. It will be provided to physicians who have training in the dating of pregnancy, the diagnosis of ectopic pregnancy and surgical abortion, and who have access to facilities for surgical abortion and for emergency treatment of complications in order to make sure that physicians can provide this drug in the future as safely as it has been provided in the clinical trial and as safely as it is being provided elsewhere.

The administration of the drug will also be subject to some limitations. Stocks of the drug will need to be kept in a secure location. Providers will have to keep a record of each dose administered, and patient information will be included in each package of the drug.

The administration of the medication will be on site and under supervision of the physician. There will be also extensive informed consent documents in each package.

In conclusion, regarding acceptability and feasibility of this method, mifepristone/misoprostol for early medical abortion is a safe, effective, and highly acceptable therapy; U.S. physicians will offer it, thereby increasing access to services; and women will have a new choice that will make abortions earlier and therefore safer for them.

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Thank you very much.

DR. DAVIDSON: Are there any questions? Dr. Azziz?

DR. AZZIZ: In regards to your data concerning the satisfaction of women who actually failed therapy, how do you potentially measure that in regards to the reliability of your data? One would assume that most women who failed the therapy would probably not be very satisfied with the therapy as a whole. Yet about half of your women who failed appear to be satisfied. Does that in any way question the reliability of the positive data?

DR. WINIKOFF: I don't think so. I think women were rating an overall experience with a clinical situation, and they were treated with respect and given a lot of information and tried the best they could to avoid surgery, and when they couldn't avoid it, they had it and they felt they had been given a fair shake. So I think they were satisfied with their experience. It was an experiential question.

DR. DAVIDSON: Dr. Zones?

DR. ZONES: As I recall in the protocol, women had to live or work within an hour of the provider's site?

DR. WINIKOFF: Yes.

DR. ZONES: That may be in the French studies.

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1 DR. WINIKOFF: I think it was work — within an
2 hour of work or home, a place where they could get
3 emergency treatment.
4 DR. ZONES: Right. Do you think that's adequate,
5 and do you think that should be on the label?
6 DR. WINIKOFF: As we've said before, this drug
7 essentially induces a miscarriage. If women can have
8 miscarriages in any given place with safety, they can have
9 medical abortion. The U.S. health care system is adequate
10 to deal with the kinds of emergencies that we have seen in
11 this trial and that the French have seen. I think that
12 that's more than adequate.
13 DR. DAVIDSON: Dr. Henderson? Or Dr. Kosasa?
14 DR. KOSASA: I just wondered, is it available in
15 pharmacies in Europe right now?
16 DR. WINIKOFF: To my knowledge, not. To my
17 knowledge, it is distributed directly to the clinics that
18 provide it.
19 DR. HENDERSON: I actually have a couple of
20 questions. The first, at the beginning of your
21 presentation, you said that 60 percent of the patients
22 actually preferred the medical termination of pregnancy.
23 Was this the general population or was this the population
24 who had already had a medical and a surgical termination?
25 DR. WINIKOFF: This is a meta-analysis of studies

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1 that were done in other countries in which women were
2 offered a choice.
3 DR. HENDERSON: Had they had a termination?
4 DR. WINIKOFF: No, this is the whole population.
5 It's all takers. This is just a generic — it's all
6 takers, and the actual range is pretty much 60 to 70
7 percent.
8 DR. HENDERSON: Okay. You mentioned that during
9 the time that women waited to bleed or their bleeding was
10 observed by the providers, they had contraceptive
11 counseling. Do you have any indication of how effective
12 that was, how many women before they had this medical
13 termination used contraception and if that changed after
14 they had the procedure?
15 DR. WINIKOFF: We will be able to look at some of
16 those issues more clearly from the individual patient data
17 when the data are available to us. Now I have the focus
18 groups from the providers, who said that the providers
19 thought it was a good experience and that they were able to
20 give more information to women. But we don't have the
21 patient data on that yet.
22 DR. HENDERSON: Okay. And you mentioned that —
23 all the things that have to be required in order to have a
24 practitioner use it. It seems to me that you're pretty
25 much excluding family practitioners and other primary care

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providers who are not OB-GYNs. Is that not a market that would need to be addressed, and if people have to be able to do all these things that family practitioners and pediatricians may not be able to do, how do you get them access to OB-GYNs, essentially?

DR. WINIKOFF: I'm not an OB-GYN, and I can do all those things. Most American physicians are trained to do all those things.

DR. HENDERSON: Doing surgical suction?

DR. WINIKOFF: Training in surgical -- it doesn't mean they currently do it.

DR. HENDERSON: Suction in termination?

DR. WINIKOFF: Training, because D&C, after all, most medical students know how to do that.

DR. HENDERSON: Mmm, okay.

The last thing --

DR. WINIKOFF: Not necessarily for abortion, but the surgical procedure is the same.

DR. HENDERSON: The other thing is, you want physicians to essentially manage the pharmaceutical, and how -- if that's going to be your primary mode of distribution, I wonder how you're going to train physicians who are just now dealing with managing medical records more accurately and appropriately, to now have them held accountable for managing pharmaceutical drugs that have to

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recorded and accounted for.

DR. WINIKOFF: Actually, this is very parallel to how the IUD is provided, and physicians do that. Physicians now manage narcotics which actually have legal restrictions on them that are more stringent. So I don't see why it should be a problem. But, obviously, it is something that one has to consider as one goes, and if there are problems, we would have to solve them. But I don't anticipate that that would be a problem.

DR. DAVIDSON: Are you finished?

DR. WINIKOFF: I understand in Europe it was distributed that way. Why have you consciously elected to eliminate the pharmacy as a means of controlling and distributing it to a variety of people and not just people who seek out a distributor?

DR. WINIKOFF: Do you mean the pharmacy on the street or the pharmacy in a hospital?

DR. HENDERSON: Any pharmacy. The pharmacy system that we have in the states.

DR. WINIKOFF: Well, it seems to me more efficient to control the distribution through the provider who has to provide it, because if it is in a pharmacy, then the woman would go get a prescription and bring it back. It didn't make kind of logistic sense. But this is not to that these guidelines -- these are guidelines that we

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think are wise to start with. It doesn't mean to say that with greater experience in the American context, we can't have a more tailored distribution system as it evolves. Certainly we don't intend for any of the usage to be set in stone. As the scientific data are not set in stone and as more information becomes available, all kinds of things can be inserted into the information and changed.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: Several questions, Mr. Chairman.

In your proposed labeling the agency has received, you have that the patient must be able to reach emergency medical facilities equipped to provide surgical termination of pregnancy, blood transfusions, and emergency resuscitation if necessary within one hour of home or work during the treatment procedure until discharged by her physician.

Did I understand you to say that that was not any longer going to be a requirement, or is that in fact a requirement?

DR. WINIKOFF: As I understand it, everything that you have in the labeling still stands.

DR. KESSLER: So that requirement stands.

The second question. In just looking at, in your presentation, on the focus groups -- I assume that is in the interviews -- you list a lot of positive comments about

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control, natural, avoidance of surgery. Those were your headings.

DR. WINIKOFF: The patient.

DR. KESSLER: Those were the patient comments. Can you give us a sense of the negative statements, if any, that you have received?

DR. WINIKOFF: Some people commented on the amount of blood they saw, that they hadn't expected -- the ones who saw more blood than they expected. Some people commented on the length of staying afterwards, after the misoprostol. They didn't feel they needed to stay that long, and they felt that was an encumbrance.

Some people wished they could have taken it at home. There, I mean, that was sort of the general range. Some people commented on whatever side effects they may have experienced that they didn't like. Basically, there were a lot of positive comments and not as many negative comments, I have to say.

DR. DAVIDSON: What about the time and inconvenience of these multiple visits?

DR. WINIKOFF: Yeah, the time was commented upon in a couple of ways. The length of the second visit was the main obstacle. The second -- people didn't -- I mean, this is a self-selected group. It was offered the method knowing that they would have to come. So for the people

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who were offered the method, that wasn't such a big problem, but after experiencing the waiting in the clinic, some people felt that it was too long.

DR. DAVIDSON: Did you have any —

DR. KESSLER: One last question. If you look at -- going back to Dr. Bardin's slide on the serious adverse events both in the French trials and the U.S. trial, if you look at hospitalizations or transfusions, is there any way when you look at those to suggest how they could be prevented, how any of these — does the distribution scheme help prevent any of those serious adverse events?

DR. WINIKOFF: I think counseling women on the amount of bleeding and helping them to assess when they should come back is very important. The more we learn about this drug, probably the better we'll be able to communicate with women about those issues.

People need to come back to the providers who provide the method so that people are familiar with when to advise them to have a surgical termination or when they need further treatment and when they can wait, and as we said, as people gain experience with the method, it becomes very important that these issues, as you'll hear from Dr. Newhall, are very striking to the providers of the method.

So we need to communicate these issues about what

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expect to the patients so that they know how to manage the situation in conjunction with the providers.

DR. DALING: I have one question.

DR. DAVIDSON: Dr. Daling?

DR. DALING: Did 100 percent of the patients come back for the second and the third visit?

DR. WINIKOFF: Yes.

DR. DALING: Amazing.

DR. DAVIDSON: Dr. Azziz?

DR. AZZIZ: Dr. Winikoff, just to come back to the comment that Dr. Henderson brought up in regards to the use by physicians who are not surgeons -- and I disagree strongly; there is no training in D&Cs other than surgical specialties. But in your recommended labeling, it simply states that patients should live within an hour of a surgical facility that does not have to be the same facility that they had the medications.

DR. WINIKOFF: Right.

DR. AZZIZ: Is that correct?

DR. WINIKOFF: That's correct.

DR. AZZIZ: So there is no exclusion of family practitioners and internal medicine? There was that impression when you responded earlier.

DR. WINIKOFF: No, no, I didn't mean to. It was a question that implied that. I certainly didn't mean to

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respond that way. We feel people need to know when a person needs surgical intervention and to be able to get it. We don't mean to imply that people all have to be able or be ongoing providers of surgical methods.

DR. AZZIZ: Thank you.

DR. DAVIDSON: Yes, Dr. Harrigan?

DR. HARRIGAN: I just have a question about the 800 people in your sample. Did that include any of the women who had adverse effects that were in the table of severe adverse —

DR. WINIKOFF: Yes.

DR. HARRIGAN: It did?

DR. WINIKOFF: It includes all the women equal to or under 49 days LMP for which this approval is being sought in the American study.

DR. HARRIGAN: I thought the American study was 2,121.

DR. WINIKOFF: Yes. Yes, but this is all the women — that study goes to 63 days. So this is all the women — it's a subset of the women within that study, the women who had 49 days or less LMP from that 2,121, which is about 800, 797 to be exact.

DR. HARRIGAN: Okay, thanks.

DR. DAVIDSON: Any further questions? Dr. Jones?

DR. JONES: You mentioned that there was no

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difference between racial and ethnic groups on satisfaction?

DR. WINIKOFF: Yes.

DR. JONES: This may be jumping the gun, but were differences found in these various social status-type groups on other variables?

DR. WINIKOFF: I only looked at the acceptability data. That's all that was available to me now. We'll have to look at the other things later. But with regard to all these acceptability questions, there were no differences found.

DR. DAVIDSON: Any further questions? Dr. Henderson?

DR. HENDERSON: Before we're done, is there any plan to give us demographics on the 2,121 patients who were in the States, the racial, the smoking histories, or the method of payment of any of these women? Just the demographics. I understand that you don't have the results, but —

DR. WINIKOFF: It's about a third, as I mentioned, DR. HENDERSON: Right. You said —

DR. WINIKOFF: Other than Caucasian, as recorded as other than Caucasian.

DR. HENDERSON: Right, but Asian, African-Americans —

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DR. WINIKOFF: That third is split, and I have the data. I can -- but it is all preliminary data and we --

DR. HENDERSON: And method of payment or any smoking history?

DR. WINIKOFF: Smoking history I don't have. The method of payment is -- it's method of usual payment for medical care, and many people had multiple answers. So it's going to be hard to disaggregate that data well. We'll have to look at it a little bit better.

DR. DAVIDSON: In the world of acronyms and few syllables, these two drugs are quite a repetitive mouthful.

[Laughter.]

I wonder, have you some abbreviated means of referring to this?

DR. WINIKOFF: No.

[Laughter.]

DR. DAVIDSON: Your answer is --

DR. WINIKOFF: My answer is no. We would love it. But the ones that we've come up with or that other people have tried out haven't worked for various reasons. But we look forward to having an actual trade name at some point that will be simpler.

DR. DAVIDSON: Okay.

DR. WINIKOFF: But you saw Dr. Robbins' slide had

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I-F. Some people say "mif" sometimes.

DR. DAVIDSON: Okay. Thank you very much. I will not lean to my temptation.

[Laughter.]

Okay, could you continue your formal presentation?

DR. WINIKOFF: Sure, thank you. I would like to introduce to the panel Dr. Elizabeth Newhall from Oregon. Dr. Newhall is one of the investigators of the clinical trial, and she will discuss her experience with this regimen.

DR. NEWHALL: Good morning. And yes, we did call it MEM.

[Laughter.]

I'm happy to have the opportunity to share with you my experiences with mifepristone in Oregon.

I am a board-certified obstetrician-gynecologist. I am a 1979 graduate of the University of California at Davis, and I began my career as an emergency room physician prior to turning to gynecology in 1984. I served on the faculty at Oregon Health Sciences University before beginning my private practice in 1990.

Concurrently, for the past eight years, I have been a provider of abortion services and the medical rector of the Downtown Women's Center, where we conducted

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the Oregon portion of the mifepristone trials.

Beginning as a pressed birth control counselor in the early 1970s, I have been a participant in women's health care for 23 years.

My experience with mifepristone is solely as an abortifacient. However, like my colleagues, I am excited about its other clinical uses in gynecology.

Simply put, mifepristone is an effective, safe, well-tolerated medical abortifacient. Moreover, American women very much want the option of medical abortion available to them. Already familiar with the monthly process of uterine emptying, women who choose mifepristone perceive the process as more natural and much less scary than a surgical procedure which in no way aligns so closely with their endogenous physiology.

Clinically, a mifepristone-induced abortion is identical to a spontaneous miscarriage, except that it is quicker. Biochemically, it is not dissimilar, in that placental support is withdrawn and then the misoprostol engages the sensitized uterus in expelling the products of conception.

We conducted our trials at the Downtown Women's Center, which is on the ninth floor of a downtown office building in Portland. We serve women of broad ethnic variety there. Women began calling for this option as soon

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as RU-486 was in the news and in huge numbers as soon as it became known it would be available in Oregon.

They still call regularly, even though the studies have been over for a year, because so many women seek the option of early pregnancy termination.

Women who met the screening parameters presented on Monday afternoons for counseling, consent, dating, ultrasound examination, and then met privately with the physicians for examination and discussion.

Following this, they took the mifepristone and went home. On Wednesday mornings, they returned for the misoprostol dosing, where, in our erstwhile recovery room, we had folding cots set up in two facing rows, sort of M*A*S*H style, where anywhere from six to twelve women began their expulsions together.

I had predicted that women would reject the notion of having an abortion as a group experience. However, it turned out to be completely the opposite. There was a lot of group support, a lot of camaraderie, and a lot of conversation between the women really helping themselves through this process, and the group turned out to be (an) unanticipated advantage to the method.

The usual experience was, about an hour or two after taking the misoprostol, sometimes immediately, cramping and bleeding began, both a bit more intense than a

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regular menstrual period. This lasted about one to two hours. Both let up noticeably. With a somehow distinct episode of bleeding, almost all the women knew when their expulsions were complete, although none were able to discern any difference between the blood -- or see any tissue. They all just saw blood and blood clots.

The women read books, they played cards, they talked about politics, they laid quietly and looked out the window at downtown Portland. Some were sad, some were pensive. They drank tea and made frequent trips to the two bathrooms, which, incredibly enough, were adequate for all the women.

Less than half the women took a pain pill or two and very rarely -- you know, maybe every three weeks or so -- there was a woman who was so uncomfortable that she required an injection for either pain or nausea.

The difference in an afternoon spent in surgical abortion as opposed to an afternoon or morning spent in medical abortion was really very noticeable in the amount of adrenaline generated both among the patients and the staff who cared for these women.

After completion of the expulsion and ultrasound documentation, many women just had to sit around and wait for the four-hour observation time to pass. I can remember only one woman who remained after the four-hour time period

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because she was so uncomfortable, and we ended up doing a suction on her by the end of the day simply to end her cramping, not because of any bleeding or medical necessity.

The nurses who tended these women, while completely capable of handling all aspects of surgical abortion independently, had rarely if ever witnessed the amount of bleeding that attends a spontaneous miscarriage or even a heavy menstrual flow.

In the surgical abortion setting, that amount of bleeding is not long tolerated. And so, initially, it was hard for them to stand by and watch, much less be reassuring, as they knew that their standard process would end it in about a minute.

The learning curve was very rapid, however, and the flow dropped very quickly to a more familiar level. They relaxed and were educated.

Those of us with wider experience in reproductive medicine who deal regularly with births, miscarriages, spontaneous loss and even fibroids were much more comfortable from the beginning.

Physicians who already work in these areas will have much less of a learning curve in this sense. They know that women regularly bleed heavily for short periods and almost never incur significant anemia or other ill effects.

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Our average drop in hemoglobin was slight to minimal. We always check hematocrits prior to an abortion of any kind, but we never deny abortion to women with anemia because birth poses a much greater risk of blood loss.

Any facility or physician that currently provides care to women having miscarriages is quite adequately prepared to handle women undergoing medical abortion. The women themselves were generally quite comfortable with the amount of bleeding, needing at most reassurance that it was as expected.

We had no infections, we had no uterine damage, we had no ectopic pregnancies, and we had no transfusions.

There were a few women who became intolerant of the sometimes prolonged light bleeding. Abortion providers again are facile with the ultrasound at detecting even small amounts of uterine debris and are used to offering women with surgical abortions resuctions for the same symptoms following a surgical abortion, where again no bleeding is what we prefer.

Because of the political atmosphere being so scrutinizing around abortion medicine and because everyone is very interested in having satisfied patients, women are very coddled in our clinic and are encouraged to participate fully in their decisions and are given all

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options at all times about anything that they want.

This and the safety and success of our surgical approach made us more quick, I am sure, than our European colleagues to offer suction for provider and patient convenience rather than out of overt medical necessity, especially since, in Europe, most D&Cs are done under general anesthesia, whereas here, at least in our clinic, the vast majority are done with the patient awake. I am certain, as our experience grows, the number of suctions will lessen.

The women who did come to surgical intervention despite having preferred initially to avoid it were very accepting when it became obviously the right thing to do. Accepting surgery as an indicated backup procedure was much more palatable than choosing it as a primary procedure. No women refused, and most did not have an ongoing pregnancy.

Which brings us to why women want mifepristone and, indeed, the option of medical abortion in general. While mifepristone has been delayed, more and more women are calling, seeking and obtaining medical abortions with an alternative drug which is much less preferable than mifepristone.

The reasons women have for choosing medical abortions are as varied as women are. Some reasons are conscious, some not. They include a general fear of

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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

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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.

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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.

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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

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

[Applause.]

DR. DAVIDSON: Are there any questions?

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

DR. NEWHALL: We had 176 in Oregon.

DR. HARRIGAN: 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.

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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 is is okay. And, really, I am impressed in my experience

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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

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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

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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.

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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 vision

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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

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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

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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

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ifferent 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 s metabolized quite extensively, probably by the liver,

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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

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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

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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,

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were 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.

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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.

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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

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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.

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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

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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,

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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

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misoprostol. We found that 210 subjects satisfied these criteria.

Two hundred eight of these subjects experienced a mplete 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

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bjects 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 monly reported adverse reaction was painful contractions

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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

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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

th 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

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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.

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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.

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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

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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

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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 --

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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 1,200-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 holding yes. All we have is their data on the safety

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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 --

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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

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

DR. RARICK: Again, I think the protocol lusion 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

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t 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. ZOLES: 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

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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.]

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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

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

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

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

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

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

"Speaking to you as a practicing obstetrician and ember of Congress I am concerned that the health and ossibly even the lives of tens of thousands of American omen will be jeopardized because the RU 486 prostaglandin ortion technique is being rushed onto the market without ufficient testing of an objective scientific and medical valuation by the FDA.

"The citizen petition filed in February 1995 by 3 members of Congress raised many extremely important and

id issues that must be addressed prior to approval. I ould like just to highlight here two particularly roubling ones."

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

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

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

1 the woman in jeopardy of having to have surgery." This is
2 citizen petition pages 23 to 27.
3 "Another hazardous situation occurs with ectopic
4 pregnancy. RU 486 could induce bleeding and give a woman
5 with ectopic pregnancy the erroneous impression that she
6 was no longer pregnant. If the woman fails to return to
7 the abortion facility to verify that she is no longer
8 pregnant the ectopic pregnancy would continue to grow and
9 possibly endanger her life when it ruptures the fallopian
10 tube.
11 "The lack of an effective means to ensure an
12 adequate level of patient compliance is a serious draw back
13 and, as the citizen petition noted, 'Even under the
14 carefully controlled conditions of a clinical trial patient
15 non-compliance has been a problem.' For example, in a
16 trial in the United Kingdom published in 1990, 9 women were
17 lost to follow-up before the abortionists could confirm
18 that the abortion was complete, 9.35 percent of the women
19 in the study failed to return for follow-up after
20 administration of the prostaglandin and 21.77 percent did
21 not return 9 days after receiving RU 486 and prostaglandin.
22 "More over, in the U.S. there is no reason to
23 expect that the prospects for patient compliance would be
24 any better than overseas. For example, Dr. Suzanne Pupema,
25 owner of a Seattle abortion facility, participated in the

1 RU 486 prostaglandin trials, she explained in the April 12,
2 1993 American Medical News that even though U.S. abortion
3 facilities routinely include follow-up visits in the price
4 of an abortion, 'We're lucky if 30 to 40 percent of these
5 patients ever return.'
6 "My question is given the current lack of follow-
7 up by U.S. surgical abortion providers and the problems
8 that many non-english speaking, uneducated women would have
9 understanding the instructions how will the FDA ensure that
10 women will comply with the complicated 3 visit RU 486
11 procedure?
12 "If I had more time I could address the hazards
13 that RU 486 poses to women with common pre-existing medical
14 conditions, the dangers to unborn children from exposure to
15 RU 486 and prostaglandin and the lack of studies on the
16 impact of women's future facility of taking these 2
17 powerful synthetic hormones.
18 "Please keep me informed of the status of the
19 FDA's review of these issues. Thank you."
20 DR. DAVIDSON: Thank you very much.
21 DR. CORFMAN: The next speaker is Lisa Kaeser for
22 the Alan Guttmacher Institute.
23 Alan Guttmacher Institute - Lisa Kaeser, J.D.
24 MS. KAESER: Good afternoon. I am Lisa Kaeser,
25 representing the Alan Guttmacher Institute, an independent,

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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

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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.

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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

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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

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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

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multaneously 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.

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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,

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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

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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

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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

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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

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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

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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

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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

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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

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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

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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.

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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

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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

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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

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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

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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

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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

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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' pocytes 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.

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

Psychosocial consequences of divorce and iolence 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.

Concerning risk of malformation of babies who survive RU 486:

Numerous malformed infants are reported following prostaglandins.

Premature 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.

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ich 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.

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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

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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

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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

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surely.

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

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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

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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,

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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

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e 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.

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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

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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

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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

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ry 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 lled for its introduction.

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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

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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

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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 invasive 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

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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

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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

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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

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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 complete 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

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proved 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

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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

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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

abortion providers and to share with you our experiences with mifepristone.

The National Abortion Federation was established 1977 as a professional association of abortion providers committed to ensuring that abortion services remain safe, legal, and accessible to all women. NAF's members provide about half of all abortions in the United States each year.

Several NAF members, including myself, participated in the Population Council's clinical trial of mifepristone. Our experience matched that reported in other countries. Mifepristone is a safe and effective forum of early abortion which should be an option for women wishing to terminate a pregnancy.

As you are aware from this morning's presentations, mifepristone blocks the action of progesterone, a hormone needed to sustain a pregnancy, and in trials to date has been proven safe and effective in terminating early pregnancy.

Our experience during the clinical trials was consistent with the experience in Europe. The drug was quite safe and effective and women who participated were generally very positive about this method.

I believe one of the reasons medical abortion with mifepristone has been and can be successful relates to the thorough counseling that both providers and women

ceive. As a provider I knew what to expect and how to care for women who were going through this process. There were no unexpected side effects and at no time did I feel that my patients were in danger. Equally as importantly, my patients knew what to anticipate and as a result felt confident using the drugs.

Many of the women in the clinical trial at my site expressed their strong support for the drug because it allowed them to participate in and have a sense of control over this experience. It is worthy to note that, in my opinion, my patients did not feel themselves to be pioneers or advocates, rather, they were women who had requested a pregnancy termination and who, after thorough counseling, simply felt that this method best met their needs.

As a doctor I believe that not only is mifepristone safe and effective but for some women it may be the most appropriate means of terminating a pregnancy. In some settings, especially in resource poor settings such as the developing world, legal access to mifepristone may result in improved health care for women who are exposed to and some times die from unsafe and ineffective abortions. Approval by the FDA of mifepristone would undoubtedly improve access to safe and effective abortion worldwide.

As you know, mifepristone is the culmination of many years of research. It has been tested in both

developing and industrial countries by the Population Council and the World Health Organization. The governments of France, England and Sweden have all approved the use of mifepristone after their own rigorous clinical trials and worldwide over 200,000 women have used this non-surgical method.

Mifepristone could also be used in treating several other conditions related to pregnancy and other medical problems such as breast cancer. With so many potential uses and impressive and efficacious record we hope that mifepristone will be favorably reviewed by the Food and Drug Administration. Thank you.

DR. CORFMAN: The next speaker is Susan Wysocki, speaking for the National Association of Nurse Practitioners in Reproductive Health.

National Association of Nurse Practitioners in Reproductive Health, Susan Wysocki, R.N.C., N.P.

MS. WYSOCKI: Members of the Advisory Committee on Reproductive Health Drugs, good afternoon. I am Susan Wysocki, President of the National Association of Nurse Practitioners in Reproductive Health and I am a certified women's health nurse practitioner.

NANPRH is a national organization representing nurse practitioners in obstetrics, gynecology, and women's health. We have no conflict or financial interest in this

product.

You have heard testimony about the medical safety of mifepristone. I would like to talk to you today about the use of mifepristone from a nurse's perspective.

Nursing's tradition is to care for patients from a holistic perspective, taking in consideration a patient's physical, emotional, and spiritual needs. Mifepristone, while not an ideal method of abortion for every woman, does have some distinct advantages and go beyond its medical safety.

In contrast to some who argue that medical abortion is too easy in most respects medical abortion is much less easy. There are three or more visits to a physician and two or three days during which a woman experiences the termination of her pregnancy versus one visit for a surgical abortion which lasts a matter of minutes and one visit for the follow-up exam.

One might ask why a woman would choose a medical abortion over surgical abortion. The difference is who is in control. With medical abortion the woman swallows the pills from her own hand, it is her body that is doing the work of aborting a pregnancy, she is a more active participant of the process, she experiences the abortion, she feels her body respond.

My colleagues who have provided nursing care to

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these women report that even when women experience side effects the control they gain from being part of the process greatly outweighs other considerations. My colleagues report that these women seem to integrate the emotional and spiritual aspects of abortion during the few days after they have taken mifepristone. The patient's reactions seem to be evidence of a greater ownership of the process.

Medical abortion is not for every woman seeking abortion. Regardless of the method of abortion chosen, surgical or medical, the vast majority of women process the emotional and spiritual aspects in a very short period of time, there are exceptions of course. Abortion does not solve the grief of a failed or abusive relationship, it won't make the time a woman had intercourse in a forced or compromised situation away, it does not solve a dysfunctional family environment or a partner's drinking problem.

As nurse practitioners in the field of reproductive health we help to prevent unintended pregnancy, whether it is helping an individual to practice abstinence or providing effective contraception. We provide women centered care in order to help promote self-esteem, to say "no" when she wants to, insist on the use of condoms, and let her make her own choice if she becomes

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pregnant unexpectedly.

There is no perfect method of contraception for the over 30 years that a woman can conceive, not one. Over 50 percent of women who become pregnant unintentionally are using contraception. Women's motivation, together with the care provided by health care providers across this country contributes to the miracle that there are not millions more of abortions. The odds are overwhelming.

Based on mifepristone's effectiveness and safety NANPRH requests that this committee approve its use. American women should have this option for terminating their own pregnancies. Thank you.

DR. CORFMAN: The next speaker is Donna Gary for the National Council of Jewish Women.

National Council of Jewish Women - Donna Gary

MS. GARY: Good afternoon. My name is Donna Gary. I am a National Vice President of the National Council of Jewish Women. There is no financial connection and no one has paid my expenses. I am a volunteer.

The National Council of Jewish Women is a non-profit volunteer organization with 90,000 members in over 500 communities nationwide. I have come before you today to urge swift approval of the New Drug Application to the FDA for mifepristone to be used for medical abortion.

The National Council of Jewish Women strongly

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supports the enhancement of reproductive health options for all women. Mifepristone has been proven worldwide to be a safe, early and effective non-surgical method of abortion. Clinical trials conducted over the last decade in France, Sweden, and the United Kingdom, along with additional clinical trials in the United States, have consistently shown that mifepristone is a viable non-surgical early abortion method.

As evidenced by the nearly 200,000 women in Europe who have chosen to use mifepristone, women trust this procedure, and many want to use this method as an alternative to surgical abortion when terminating a pregnancy. Don't women in the United States deserve the same reproductive health options as women in these countries?

We believe that FDA licensing of mifepristone will result in a significant step towards improving reproductive health options for women in this country. The introduction of mifepristone would have a profound effect on women's health in the United States. Not only would it provide women with a safe, non-surgical method to terminate pregnancies early on, but mifepristone could also be used in treating a wide range of medical conditions affecting women including breast cancer, endometriosis, and uterine fibroids.

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The availability of mifepristone in the United States would likely improve access for women seeking abortions. Often women must travel long distances to obtain an abortion and often endure harassment and violence when seeking clinic services. Making mifepristone available in this country would give women the option of locating practitioners closer to their homes who are wiling to provide medical abortions.

The National Council of Jewish Women strongly supports "every female's right to reproductive choice, to safe and legal abortion, and to the elimination of obstacles that limit reproductive freedom." On behalf of the National Council of Jewish Women, I strongly recommend approval of mifepristone for licensing in the United States. Thank you for this opportunity to testify today.

DR. CORFMAN: The next speaker is Janice Erickson for the National Organization for Women.

National Organization for Women, Inc. - Janice E. Erickson

MS. ERICKSON: Thank you very much. I am Director of Government Relations and Public Policy for the National Organization for Women. I am speaking here today for the NOW Foundation. We have no financial interest in this drug.

NOW is the largest feminist organization in the

country, with over 275,000 members in 700 chapters throughout all states. We have a long history of advocacy for keeping abortion safe and legal and accessible.

NOW believes that mifepristone should be found safe and effective by this advisory committee and should ultimately be approved by the Food and Drug Administration for general use in the United States. Sixteen years of testing and clinical experience with mifepristone in Europe and America have provided abundant evidence that the drug is effective in terminating in early pregnancy with very few side effects.

Mifepristone has been safely and successfully used by nearly 200,000 European women, approved by the governments of France, Sweden and the United Kingdom, the RU 486 story is one of sound medical technology responding effectively to meet vital patient needs.

We are fortunate in the United States to be able to benefit from the European experience. It is our understanding that the U.S. clinical trial findings are very comparable to those from France as regards safety and efficacy.

We expect that this advisory committee's conclusions will be based on a rigorous examination of the available French and U.S. data and the final decision by the Food and Drug Administration will be based exclusively

strong scientific evidence in favor of approval for mifepristone for general use.

Advances in the medical research of reproductive health have been tragically slowed and even stopped in this country. Women and the general public have suffered immeasurably as a result. We must move forward. A majority of the American public does not want to see safe and effective improvements denied to anyone, as private surveys show.

Even a substance proportion of the abortion rights opponents surveyed are supportive of early medical abortions. A safe, effective, early abortion drug may begin to heal the wounding divide that has been created in the public over this procedure.

The problem of accessibility to abortion services has been a vexing one for reproductive rights advocates. Mifepristone offers the best solution yet to expanding the pool of providers and ultimately to bringing the cost of the treatment well within the means of most women.

Successful trials on mifepristone as a method for early abortion in Vietnam, Cuba, China, and India by the Population Council as well as trials by the World Health Organization in Chile, Germany, Hungary, and other parts of the world show that there are no differences in the rates safety, efficacy, and acceptability when comparing

racial or ethnic groups. This would indicate that there would be wide acceptance in use of this important drug worldwide.

As an organization concerned about the health of all women we are eager to see this country move forward. Such critical health problems as endometriosis, breast cancer, uterine fibroid condition, which effect millions of women could potentially benefit from further research on mifepristone. An aging U.S. population could also benefit from the other research and applications that could be found on this drug.

Finally, it should not be overlooked that mifepristone, through expanded research and development in the United States could make a tremendous contribution to international contraception and fertility treatments, especially in the developing world.

America's incomparable medical research infrastructure and financial resources, coupled with FDA's rigorous and independent regulatory function can help ensure for the world a safe and effective drug through mifepristone. Thank you.

DR. CORFMAN: The next speaker is Cynthia Pearson, speaking for the National Women's Health Network.

National Women's Health Network - Cynthia A. Pearson

MS. PEARSON: Good afternoon. My name is Cindy Pearson, Executive Director of the National Women's Health Network.

The Network is a nonprofit women's health advocacy group, supported by over 14,000 and 400 organizational members. The network does not accept financial support from pharmaceutical companies or manufacturers of medical devices and has no financial interest in this.

Ellie Smeal aptly described the feminist community's some times critical view of the medical profession and commonly used drugs, devices, and procedures. As many of you know all too well, if there is any one organization that exemplifies that attitude it is the National Women's Health Network.

[Laughter.]

I am here to tell you today that we believe it has been well demonstrated that mifepristone used with misoprostol for early abortion is effective and its short term safety in the women's study is well documented.

We also believe that abortion is a woman's right and the medical profession has a duty to provide abortion in a safe and acceptable manner. We would like to focus our remarks in this short time today on the safety allegations made by groups which, unlike the Network,

oppose abortion.

The Network is a diverse organization. More than half of the members of our board of directors are women of or. The FDA in the past has heard from anti-abortion groups asking that the FDA not approve mifepristone and misoprostol because it is unsafe for women of color.

It is true that women of color were not represented in the pivotal French trials and the Network previously raised questions about the unknown effect of these medications in women of color but we were happy to hear, presented today, data which demonstrated that women of color, who made up approximately one-third of the women in U.S. trials, describe their experience in exactly the same way as did white women.

While we understand that these are not medical reports we are willing to trust women's own description of their experience and are reassured by these data. We believe that there is no reason at this time to oppose approval because of concerns about women of color's safety.

Anti-abortion groups have also asked that the FDA not approve mifepristone plus misoprostol because it will increase the likelihood of developing breast cancer. Breast cancer is an issue on which the Network is expert. In January of 1994 we were the first women's group to release a physician paper on the possible link between

rtion and breast cancer.

We reviewed the evidence and found that the link between abortion and breast cancer had not been established. In contrast to Dr. Brind's description earlier this afternoon that the preponderance of the evidence demonstrates an increased risk of breast cancer our review found that there are over 70 studies which have data on abortion and breast cancer. Fewer than 30 of these studies have been published to date and of those published about half found an increased risk while half found no increase at all.

Also in contrast to Dr. Brind's claim it is our understanding that another meta-analysis, one which will include all data, both published and unpublished, is being conducted and that it appears to be finding no increased risk.

To claim that abortion increases the risk of breast cancer is to misrepresent data in an effort to frighten women and we believe that the FDA need not even consider this issue when deciding whether or not to approve mifepristone.

Finally, anti-abortion groups have also claimed that mifepristone plus misoprostol should not be approved because there are or maybe long term risks associated with use. The Network has consistently raised questions

about the long term safety of drugs given to women. Our typical concerns are much diminished in this situation.

Mifepristone is intended to be used once, or at most a few times, and has a short half life. Long term effects are most often caused by drugs which are used long term, for example, Cytotec which we have just heard so much about typically is used on a long term basis.

Misoprostol has -- given this reassuring information we believe that approval should not be delayed while we search for the final answers about long term safety. The Network believes that it would be prudent for the FDA to require post-approval studies with long term follow-up but we want to emphasize thought that our recommendation is made on general principles, not because of specific concerns based on any biologically plausible mechanisms.

We also want to re-emphasize that we believe there are adequate safety data to approve mifepristone and misoprostol now. Mifepristone is an effective method of abortion which expands the options of women desiring pregnancy termination. We applaud its consideration by this committee and recommend its approval.

DR. CORFMAN: Next speaker is Susan Hill for the National Women's Health Organization.

National Women's Health Organization - Susan Hill

MS. HILL: Good afternoon. I come to you today as an abortion provider from the trenches. I am the President of National Women's Health Organization, a private company that manages eight abortion clinics in eight states. The mission of our company since 1976 has been to provide abortion services in under-served areas of the United States.

We were the first abortion provider in rural Indiana in 1978. We were the first abortion clinic in Delaware in 1978 and the only clinic in that state for 10 years. We were the first abortion clinic in North Dakota in 1981 and we are still the only clinic in the state. In 1995 we opened an abortion clinic in Jackson, Mississippi. We are one of the two remaining clinics in the state of Mississippi.

In January 1973, when I started working in the abortion service field, I believed that by 1996 American women would be able to receive abortion services in their private physician's office with all the privacy and confidentiality that that would provide. I could not have guessed or dreamt that instead of more providers there would be less and that their very lives would be threatened everyday by providing abortion services.

Today, American women obtaining the legal medical service of abortion are put through a test that no American

could believe until they, their wives, daughters, or friends are in need. Women in Mississippi and North Dakota obtain services under restrictions that no other medical service would ever be required to have.

In Mississippi, the poorest state in the country, women are required to have a state produced consent read to her face to face 24 hours before the procedure by a physician only. The state requires color pictures of fetuses along with a script, produced by politicians not physicians, to be read to the woman.

Women come from the Mississippi delta, the poorest region in the state, which is four hours away from Jackson. They sleep overnight in their cars because they have no money for a hotel. I have personally counseled a family from the delta whose 11 year old had been raped and was in the clinic for a procedure. We found that family the next morning at 5 o'clock sleeping with that daughter and 2 other daughters in their car waiting to comply with the 24 hour waiting period. Certainly no American woman should be forced to obtain legal medical services in such a punitive manner.

Women in North Dakota drive 10 and 12 hours from the most distant parts of the state to get to our clinic in Fargo. They pass many cities and towns where there are doctors but no abortion services. They face the same

strictions and hardships that women in Mississippi face.

In the 23 years that I have provided services I have watched women between the ages of 10 years old to 50 go through hell to obtain abortion services. They have been screamed at, threatened, pushed, evacuated from clinics right after surgery because of bomb threats, followed home, harassed at work, and still they have made a choice that is given to them by the law of the land.

More importantly, I believe I am the only person testifying today that has worked personally with a physician who was killed for providing abortion services. Dr. David Gunn was a physician at our Georgia, Southwest Georgia rural clinic, for eight and a half years. He was forced to drive 1,000 miles a week to 5 clinics in the South because no other doctors would provide the service.

Our Columbus, Georgia clinic, open since 1974, has never had a local physician. Our Fargo clinic, open since 1981, has also never had a local physician. Our Indiana clinic has not had a local doctor since 1986. Our Mississippi clinic has no local physician. Surprisingly, our Orlando clinic in a large metropolitan area, has not had a local physician since last year.

Doctors are willing to provide abortions but they are not willing to become targets. May I just finish one last thing please? I believe with all my heart that

mifepristone could stop this ghettoization of abortion providers. Women would finally have the option of privacy in their choice. Staff and physicians would no longer be targets but once again medical professionals providing medical services.

When I first heard about RU 486, I went to France to observe its use. The French physicians asked our reactions after two days of observations. Our first response was, "It's so quiet and peaceful. This is the way medical services should be done."

On behalf of the 600,000 women our clinics have served from North Dakota to Mississippi to North Carolina, I beseech this committee to give to women the privacy and respect that this drug would ensure them. I have observed many times that women having illegal abortions in this country were afforded more privacy than women have had with legal abortion.

Please give women back the dignity that they so deserve in this country. Thank you.

[Applause.]

DR. CORFMAN: Next speaker is Ann Kolker for the National Women's Law Center.

National Women's Law Center - Ann Kolker

MS. KOLKER: Good afternoon. I am Ann Kolker, Public Policy Director at the National Women's Law Center,

a legal and public policy organization that for over 20 years, has been working to secure equality and equal opportunity for women in the work place, in educational and family settings, and in their access to health care, income and family support services. I appreciate the opportunity to appear before you today.

Central to women's equality is access to safe and legal abortion but as we have just heard, so eloquently, over the years a vocal minority has waged a relentless battle to make abortion illegal again, to intimidate women seeking services, and to drive providers out of practice, through harassment, violence, and threats to their families.

The submission by the Population Council of an NDA for mifepristone and the approval process now underway here at the FDA have a chance to change this landscape dramatically. The Center strongly supports FDA's efforts to review carefully and thoroughly this NDA and determine whether mifepristone, in combination with misoprostol, is safe and effective. We fully hope that the FDA will come to the same conclusion that has been reached by experts in France, Great Britain, and Sweden where the drug has been available for several years, if not more.

We cannot overstate the value to women of the availability of safe medical abortion as an alternative to

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surgical abortion. Use of an abortifacient drug can take place in a physician's office rather than at a clinic. Thus, women will be spared the kinds of traumas that we ve just heard so eloquently described, blockades and taunts.

The statistics are very very chilling. Indeed, in recent years nearly 40 percent of clinics experienced some form of severe violence and nearly 20 percent of clinic staff reported death threats and home picketing.

Assuming that the FDA determines that mifepristone is safe this method of non-surgical abortion has important and favorable implications for the health of women seeking early termination. Many women, as we have already heard, seeking early termination may fear the invasive nature of surgery along with the prospect of anesthesia. Taking several pills induces the abortion which then occurs in the same way as a miscarriage.

The fact that mifepristone works early in pregnancy, when abortion is safest, is also advantageous. The availability of the drug for use during the first seven weeks of pregnancy, or nine weeks at most, will act as an incentive for women seeking to end an unwanted or unsafe pregnancy to seek medical help in the early weeks.

The approval of mifepristone stands to have a beneficial effect on the number of providers willing to

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rform abortions in this country, a change that has positive implications for women's health as well.

A recent survey by the Kaiser Family Foundation found that at least one-third of OB/GYNs would add abortion to their practice if involved prescribing medication such as mifepristone rather than surgery.

Ultimately, the availability of more physicians willing to provide abortions will reduce travel time and arrangements, particularly for women in rural areas, thus, enabling these women to undergo the procedure at an earlier point in the pregnancy when it is safest.

the National Women's Law Center, which has worked with FDA over the years on newly developed methods of contraception, know that product approval decisions are based on careful review of clinical trials, scientific data and research articles by physicians and other experts.

Some who have appeared before this advisory committee earlier today presented claims and charges about mifepristone that are not supported by clinic trials and the experiences of both women in this country and overseas who have successfully and safely used this non-surgical abortion method for many years.

Thus, we urge this committee to be guided in its decision making about mifepristone by the scientific idence presented by the Population Council's NDA and

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related materials and not on ideologically motivated claims that are without scientific merit.

American women eagerly await your recommendation and hope that before the year is over the FDA will render a favorable decision on this important medical breakthrough. Thank you.

DR. CORFMAN: Next speaker is Dr. Louviere from Northeast Waterloo Family Practice.

Northeast Waterloo Family Practice - Mark Louviere, M.D.

DR. LOUVIERE: Thank you. I hope God or whoever we believe in isn't telling us something with that thunder out there.

[Laughter.]

My name is Mark Louviere. I am a board-certified family practice physician who does quite a bit of OB, about 150 deliveries a year, in Waterloo, Iowa. I am on the clinical teaching staff at the University of Iowa College of Medicine.

I have been told, and I hope it is true, that my expenses will be paid for by the Life Issues Institute, even though I am pro-choice I find it very interesting that they are willing to do that. I am ethically and morally opposed to abortion, have not done or will ever do abortions but for reasons I do not want to go into here, I

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believe that it should be safe and legal.

I am the infamous Iowa connection that has been referred to many, many times today. I will tell you that story. In November of 1994 I was called to the Allan Hospital Emergency Room in Waterloo, Iowa, for a woman who was bleeding due to a miscarriage and was in obvious shock.

A blood test showed that she had lost between one-half to two-thirds of her blood volume. For those of you who understand this, her hemoglobin was 5.8 and her hematocrit was 17.3. Her blood pressure was 90/60, her pulse was 120, she was in obvious shock.

I had thought she was having an incomplete miscarriage, but her husband took me into the hall and told me that she had taken RU 486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate D&C.

Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.

Even later that evening, 2 hours post-transfusion of those 2 units, her hemoglobin was still 6.8 and her hematocrit was 20 something. She required two more units

of blood because she was still orthostatic and symptomatic.

Because I aware of the clinic trial, the following day I called Planned Parenthood of Greater Iowa n Des Moines and notified them of what happened. I sent a complete copy of her medical chart to Des Moines. I would have thought nothing more about it and would not be here today if it wasn't until about 10 months later I read an article in the Des Moines Register that Planned Parenthood of Greater Iowa had reported, and I quote, "The clinic test of the abortion pill has ended in Iowa with no complications reported among 238 women who ended unwanted pregnancies without surgery," end of quote. They did not say anything about unsuspected complications or complications with the trial, they said there were, "no complications among 238 women." This was a lie to the people of Iowa.

I had two concerns. One was that Planned Parenthood was obviously lying to the media and, therefore, the people of Iowa. My second concern was that I had idea if Planned Parenthood was lying to the Population Council and, therefore, to the FDA.

This became a news story because I wrote an editorial, as I often do, to the Des Moines Register. Instead of printing it as a guest editorial they made it into a news story regarding my findings which was picked up

y the Associated Press and reported across the country.

The response by Planned Parenthood in this news story was rather disingenuous. They said that what they meant was that there were no unsuspected complications. I mean, I wonder if she would have died, I mean we know that that may be a complication so that would not have been unsuspected but they also said that there were no complications to the carrying out of the trial and I do not know what that means, whether people dropped their pill or they did not get hit by a car walking across the street.

I did call The Population Council and informed them of my findings and they had been told. They told me that Planned Parenthood of Greater Iowa had informed them.

Because of my concerns about Planned Parenthood of Greater Iowa lying to the media and perhaps lying to the Population Council, I have concerns about the use of RU 486 by physicians without appropriate follow-up. My concern is that when RU 486 is used some patients may experience the same untoward complications because it is used in an outpatient setting. There is no guarantee that once patients receive RU 486 they will follow-up appropriately if there is a complication.

In summary, I am concerned that all of the complication of RU 486 were not reported to either the edia or to the FDA. I am also concerned that the non-

surgical approach to abortion, due to poor patient compliance, for a number of reasons will lead to more complications than actual surgical abortion.

I thank the committee for this opportunity to appear and report my findings. Thank you very much.

DR. CORFMAN: I have been told that if we do lose power because of the storm there will be emergency lights. It will be dim but we will be able to see what is going on.

The next speaker is Mary Jasinski Caldwell for Pharmacists for Life, International.

Pharmacists for Life, International - Mary Jasinski Caldwell

MS. CALDWELL: Good afternoon. On behalf of the officers, board of directors and thousands of supporters for the Pharmacists for Life, International, I wish to thank the advisory panel for consideration of our oral testimony.

PFLI is a professional pharmacy association whose unique scope and mission is exclusively set out to defend and stand for the integrity, dignity, and sanctity of all human life from the moment of fertilization to natural death.

We differ from almost all other professional pharmacy associations in that we have no economic motive for existence.

The presumptive reason for today's hearing is to inquire into the petition for approval by the full Food and Drug Administration for use of mifepristone as an abortifacient in the United States. I am here to express the complete and total opposition and protestation by our members and supporters to any such approval for it is totally contrary to all pharmacy codes of ethics and standards from the time of Hippocrates to the present day.

Pharmacy is a life saving profession and nearly year after year we are rated as the most trusted profession by the public in an annual Gallop poll. It is difficult to comprehend that we would preserve that place of pride for very long should it become well known that we did little, if anything, to prevent introduction of mifepristone into the American health care system.

The literature on mifepristone, rightly called a "human pesticide," by the late world-renowned geneticist Dr. Jerome Lejeune clearly shows that it is hardly anything simple, effective, or safe, quite to the contrary. The extensive testing of mifepristone abroad, as well as the cryptic like secretive trials that were run here in the United States with most funding coming from the agenda driven Buffet Foundation, shows mifepristone is rather ineffective. The recent secretive trials in the United States yielded one subject who lost four pints of blood and

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nearly bled to death.

On the question of privacy, mifepristone requires three to five office visits by the woman to a licensed abortion clinic, a number of invasive examinations and tests and the taking of up to a five drug chemical cocktail. Mifepristone has a failure rate to 20 to 40 percent alone, necessitating use of a second drug, the prostaglandin Cytotec, which still results in a 5 percent abortion failure rate requiring 1 in 20 women to undergo yet another abortion procedure.

The many short term adverse effects include bleeding of up to 42 days, cardiovascular maladies, fatigue, abdominal pain, nausea, dizziness, and syncope. There are unknown long term side effects due to these drugs and the use on the womb, ovaries, adrenal glands, central nervous system, and the developing embryo.

Dr. Renee Kline summarized her position on mifepristone this way, and I quote, "Although I support a woman's right to a safe and legal abortion with good counseling, I am emphatic that this dangerous second rate drug is not a positive decision to a woman's decision making."

It is odd that the FDA consider the application for this chemical from an organization whose own non-profit status is the current subject of scrutiny by assorted

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ties and which itself is not a pharmaceutical manufacturer but rather a funded arm of the Rockefeller Foundation whose scope and vision includes negative population growth. Would mifepristone be the great wonder drug and marketing home run as its promoters say it is drug manufacturers would be fighting to introduce it.

With all of the foregoing in mind as well as the awesome grave and moral and ethical responsibility the FDA has for the approval of safe and effective drugs which are meant to heal and preserve life it would be a black letter day in the United States should this panel recommend approval of mifepristone to the full DEA.

We emphatically and categorically petition you to reject any approval of mifepristone for use in the United States of America. Thank you very much.

DR. CORFMAN: The next speaker is Gloria Feldt, speaking for the Planned Parenthood Federation of America.

Planned Parenthood Federation of America, Inc. - Gloria Feldt.

MS. FELDT: Good afternoon. Thank you for allowing me to speak. I am Gloria Feldt, President of Planned Parenthood Federation of America.

Each year our nearly 1,000 health care centers nationwide provide reproductive health care, education, and counseling services to over 5 million individuals. For 80

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years family planning services to enable people to prevent unintended pregnancies and plan wanted ones has been the heart and soul of our work.

Planned Parenthood centers provide abortion services to about 130,000 women each year. Six of our centers were part of the mifepristone clinical trials.

Every time there is a news story about medical abortion women call Planned Parenthood, the name they trust. Women ask us about medical abortion and we have to tell them, "Yes, we know it's available in Europe but we can't offer it to you here." These women are understandably frustrated.

Political reasons, not medical reasons, stood in the way of introducing mifepristone in France at first until their public health service declared it to be the, "moral property of women," and went forward with it.

We are gratified that mifepristone, which has been used successfully by more than 200,000 women in Europe, has finally reached the point of FDA consideration and mifepristone should be reviewed in the same manner as any other drug.

Strident opposition from those religious/political extremists has chilled and deep frozen critical research and testing for all kinds of health services that could help protect the fertility and lives of

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women and might also contribute to medical treatment for other conditions. I know you must be under tremendous pressure from the opponents of mifepristone and I hope that this hearing today will mark the beginning of a new era for women as they strive to plan and space their children responsibly.

The acceptability study presented today by the Population Council backs up what Planned Parenthood's physicians, nurses, and counselors have observed. Most women were quite satisfied with medical abortion. Because of the in depth counseling that they received women said they were prepared for the mifepristone process.

The side effects some women experienced did not surprise or scare them. For most women, in fact, the procedure was what they expected or better than they expected. I might add that the patient in Iowa whose situation was not exactly accurately described reported that she herself was satisfied with the procedure. Certainly there is no drug or medical procedure without some level of risk which is why we have the FDA to assess those things for us.

Unintended pregnancy itself is a tremendous problem in the United States and carries with it health risks far greater than mifepristone. We at Planned - Parenthood do our best to serve women with contraceptive

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information and services but it is imperative that American women faced with unintended pregnancy have access to the newest and safest methods of ending a pregnancy as early as possible.

Making mifepristone available will also eventually increase women's access to abortion services and make harassment and violence less effective as a weapon against women and health care professionals who serve them. That is exactly what the opponents of mifepristone are most afraid of.

In summary, our experience with mifepristone was what we at Planned Parenthood and the women we serve expected. For the overwhelming majority of women mifepristone proves safe and effective. The complications that arose were the ones that were expected and were manageable. Serious complications were rare. Most women were satisfied.

We at Planned Parenthood look forward to offering medical abortion using mifepristone. We are ready. American women are ready for this safe and effective method. Thank you.

DR. CORFMAN: Next speaker --

DR. AZZIZ: If I could have a question for a second.

MS. FELDT: Certainly.

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DR. AZZIZ: Could you clarify for a second what kind of problems that you encountered in Iowa perhaps? Clearly that was a problem either in reporting or in access to the patient's follow-up so perhaps if you could give us a little more enlightenment.

MS. FELDT: Yes. The exact situation was this, the patient was unable to return for her second follow-up exam, the third visit, due to weather conditions. She experienced this problem. Had she been able to return for the appointment that she had it is probable that a surgical abortion would have been provided for her at that time and it is highly probable that that would have eliminated the problem or she would not have had the problem that she had.

The complication was in fact, immediately in fact the same day, reported to the Population Council which the next day reported it to the FDA.

DR. AZZIZ: I guess what I am unclear as is was the hemorrhage event related to RU 486 treatment 2 weeks prior or was it related to a spontaneous miscarriage that occurred after a failed termination?

MS. FELDT: No, she had taken mifepristone and she had not been able to return for the third exam in the series of three.

DR. AZZIZ: The bleeding episode occurred how on after the RU 486 was administered? Two weeks? Three?

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MS. FELDT: Let me look. I actually have a time table of events which I would be happy to leave with you which would probably be better than my trying to answer it for you.

DR. AZZIZ: My only concern and we don't have to is whether the bleeding episode, which is not uncommon, severe bleeding, with incomplete abortions that occur and this may be the case as opposed to a complication related to the medication and for the committee that is an important issue.

MS. FELDT: I understand. The bleeding --

DR. LOUVIERE: Approximately two weeks later she was not able to get to her appointment. If she had been able to get to her appointment I believe she would have been managed appropriately. I had no problem with that. My feeling was that the article in the paper said that there were no complications --

[Dr. Louviere is speaking from the audience without a microphone, unable to hear all of comment.]

MS. FELDT: And it was at that approximately two week point. I do not know if that answers it. I would be happy to provide you with the exact time line of how things occurred if you would like to have it.

DR. AZZIZ: Thank you.

DR. CORFMAN: The next speaker is Dr. Lynn

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Borgatta for Planned Parenthood of Westchester and Rockland.

Planned Parenthood of Westchester and Rockland, Inc. - Lynn Borgatta, M.D., M.P.H.

DR. BORGATTA: Good afternoon, members of the committee. It has been a long afternoon, we are almost at the end.

I am a board-certified obstetrician/gynecologist and a public health physician. I am also a dues-paying member of some of the mainstream organizations that have presented earlier such as the American College of OB-GYN, American Public Health Association, and American Medical Women's Association. I am a clinical associate professor of OB-GYN at New York Medical College.

I am here today representing Planned Parenthood of Westchester, Rockland and Putnam Counties, a large Planned Parenthood affiliate in suburban New York where I am medical director. I am also representing the Association of Reproductive Health Professionals.

Our Planned Parenthood was one of the 17 sites for the mifepristone trials in this country and I would like to present some of our experience. We were honored to participate in this very important research and we support the approval of mifepristone.

Many of my feelings are very similar to those of

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Dr. Newhall who presented her experience so beautifully this morning. As experienced providers of surgical abortion services, and I have 20 years of experience yself, Planned Parenthood knows the safety of their surgical procedures and the high level of satisfaction of our patients who undergo surgical abortions.

Early surgical abortion is so safe that it is really hard to improve on such a good record. Mifepristone, however, provides an important alternative. Since mifepristone has been used by so many women before we were able to draw on the experience of others in setting up our own program. Our program did not require any additional facilities other than those that we already had as provider of many women's medical services including pre-natal care and family planning.

We found that the mifepristone abortion process is, of course, very different from a surgical abortion and we found that it was effective for almost all of the women and that there were no unexpected side effects.

Our clientele was diverse in ethnic, socio-economic, and age distribution but all of the women found the side effects tolerable and most of them found them to be relatively minor and of short duration. Women said things like, "Well, yes, I have pretty strong cramps but I have had cramps before. I have bleeding but I have

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:perienced bleeding before." When they were all done they said, "I did it."

The events and possible complications which may occur during and after a medical abortion a similar to those that may occur during and after a miscarriage. The doctor and the medical professionals who are competent at managing the events during a miscarriage have the skills necessary to manage mifepristone abortions. Since many physicians, besides just OB/GYNs, are trained to assist women who have miscarriages the availability of medical abortion can improve access to early abortion and, as you know, early abortion is the safest.

Ectopic pregnancy has been mentioned and the most successful treatment of ectopic pregnancy occurs when early diagnosis has been made and anything that brings women in earlier will assist in the diagnosis of early ectopic pregnancy.

Mifepristone was very acceptable to our patients and our staff. Those who choose it were grateful to have this non-surgical alternative and we must continue to disappoint women who want to use the method and are unable to.

In many other areas of medicine we have situations where there are several possible treatments and the United States women participate in decisions about

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their care in consultation. They decide based on the risks, benefits and acceptability and treatments are individualized.

Mifepristone provides a safe and effective way and it increases the number of choices and the natural choice is to have a choice.

DR. CORFMAN: The next speaker is Marie Bass, speaking for the Reproductive Health Technologies Project.

Reproductive Health Technologies Project - Marie Bass

DR. BASS: Thank you very much. I am Marie Bass. I am here today on behalf of the Reproductive Health Technologies Project. This project came into being almost 10 years ago because of this very product. A group of people from a very, very diverse set of backgrounds and affiliations including leaders from international population groups, family planning organizations in this country, women's health groups, feminist groups, women of color groups, there was almost nothing that everybody could agree on except that this product and the whole class of drugs to which it belongs were not progressing in this country not because of science or medicine but because of politics. This translated into fear on the part of the scientific community, cowardice on the part of industry, and at bottom a fundamental disregard for women and their

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health needs.

The project over these past nine or 10 years has worked very hard to serve as a bridge between scientists and women's advocates, health care providers, practitioners, policy-makers and others to bring many voices and viewpoints to all of the deliberations, all the questions of safety, all of the questions about whether a product like this could really be adapted practically and safely in our health system in this country which is very different from the European system. We have taken on many, many, many of the questions that have been brought up today. I think that, as many people have said already before me, this kind of process that we have been through has given people the comfort and security that it is time, it is well past time that this product should be made available to American Women.

We believe that it is very important that you consider this drug in the same way that you would other drugs. We think you are doing that. We also think that it is very important that you not delay and not be subjected to any special considerations because of the politics of abortion. We remind ourselves that abortion is a legal medical procedure in this country that some women choose. As long as that is true, any potential new method should be considered in the context of medicine and a woman's good

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alth and not politics. So we depend on you to evaluate
is product with the same careful, strict standards we
ow you will and move very quickly. Thank you.

DR. CORFMAN: The next speaker is
. Wendy Simonds speaking as a private citizen.

Agenda Item: Private Citizen Wendy Simonds,
.D.

DR. SIMONDS: Good afternoon, Chairman and
mbers of the Advisory Panel. I am Wendy Simonds, a
ciology professor at Georgia State University. The
pulation Council paid for my trip today.

One of my academic specialties is women's health.
r the past six years my research has focused on abortion.
recently completed an ethnography of an abortion clinic
ich was published as a book entitled Abortion At Work
is year. Over the course of my research, I spent a great
al of time talking with health care workers and the women
ey serve. My work leads me to believe that mifepristone
ll change the face of abortion in the United States. I
delighted that we have reached the point in this country
ere the FDA can consider approving mifepristone.

I would like to offer two points in support of
is approval. First; it is my professional opinion that
men seeking to terminate unwanted pregnancies will
rceive mifepristone as a completely new option, wholly

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fferent from surgical abortion. Many women who use
fepristone feel that they are active participants in
eir own abortions as others have testified. The provider
ves a woman the pills, but she feels that it is her body
es the work. Such an internal locus of control is
althy and helps women feel they are taking charge of a
tuation that may be upsetting.

Mifepristone abortion is less frightening to many
men than surgical abortion because it involves no
rgical instruments. It is far less invasive and affords
men more dignity than surgical abortion does.

As others have testified, mifepristone would
able women to have abortions earlier than we could if
rgical abortion were the only option. Unlike most other
thods of abortion, mifepristone can work as early in the
egnancy as a woman wants. There is no need to wait once
unwanted pregnancy has been confirmed.

Secondly, my research has convinced me that
ifepristone offers an entirely new option to abortion
oviders and other medical professionals.

In the field of abortion major technological
eakthroughs have been rare and providers are keen to
are this new choice with their clients. Mifepristone
ill also help doctors and their clients to avoid the
assment and terrorist tactics of anti-abortionists

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1 because it allows more privacy. It can be offered in a
2 variety of medical settings, not only in abortion clinics.
3 Many health care providers who do not now provide
4 abortion would be willing to offer this new method.
5 In short, I believe mifepristone offers a
6 ground-breaking and welcome abortion method to women and
7 health care providers with important sociological
8 implications for the United States. I urge the FDA to
9 approve the drug swiftly if it deems it safe and effective.
10 Thank you.
11 DR. CORFMAN: The next speaker is
12 Dr. Seymour Romney, speaking for the Society of Physicians
13 for Reproductive Choice and Health.
14 Agenda Item: Society of Physicians for
15 Reproductive Choice and Health - Seymour L. Romney, M.D.
16 DR. ROMNEY: I am Dr. Seymour Romney. I am
17 Professor Emeritus and the former Chair of OB-GYN at the
18 Albert Einstein College of Medicine and have spent more
19 than 45 years between comprehensive experience in Boston
20 and New York in obstetrics and gynecology. I have seen a
21 lot of things that we have talked about before and after
22 Roe v. Wade.
23 The Society is an organization of physicians.
24 They are a mixture of all disciplines. We are very much
25 concerned about reproductive health care and the freedom of

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1 inquiry in American medicine.
2 The Society urges the FDA to promptly approve
3 this application. The clinical benefits of mifepristone
4 should be made pharmacologically available to the American
5 public as an established safe and effective drug. Our
6 organization has an ethical and moral responsibility to
7 ensure that everyone has the knowledge, access to quality
8 services and freedom of choice to make their own
9 reproductive health care decisions. We believe that every
10 pregnancy should be an intended, wanted pregnancy.
11 Concerning mifepristone within the patient-doctor
12 relationship, the medical profession has the ultimate
13 responsibility to determine its safety and effectiveness.
14 We have seen the informed consent form employed in the
15 Population Council's clinical trials. It is accurately
16 detailed and readily understood by any women seeking a
17 noninvasive pharmacologic termination of early pregnancy.
18 That is her constitutional right.
19 For physicians the exclusion clinical criteria in
20 mifepristone protocols is the need to carefully evaluate
21 whether patients are heavy smokers or have any evidence of
22 heart disease, ectopic pregnancy, chronic liver or kidney
23 disease that could complicate her care.
24 The Society of Physicians for Choice supports
25 approving mifepristone. It is actually based on the

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extensive clinical reports of safety and effectiveness in more than or approximately 200,000 women in France, Sweden, and Great Britain, as well as promising preliminary data concerning the therapeutic value of mifepristone in a spectrum of gynecologic problems including missed menses, term and post-term labor induction, endometriosis, fibroids, and very significant promise of therapeutic benefits obtained by mifepristone's inhibiting progesterone receptor activity in patients with breast and endometrial cancer, meningiomas, and other antiglucocorticoid conditions.

In further support of the application, and to additionally document the safety and effectiveness of this mifepristone application, the Society of Physicians for Choice respectfully requests that this detailed document, which is a report by the Institute of Medicine of the National Academy of Sciences published in April of 1993 entitled "Clinical Applications of Mifepristone, RU 486, and Other Antiprogestins," again, I would point to this document which is a public instrument be included as an important reference of this hearing.

This is a comprehensive report of a committee having expertise in cell biology, pharmacology, epidemiology, or reproductive endocrinology and care of women with hormone-dependent clinical conditions. It is an

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biased evaluation of the science and the therapeutic potential of antiprogestins for numerous diseases and recommends clinical studies to further document the value of mifepristone.

The Society of Physicians for Choice believes that your committee has a commitment to the freedom of scientific inquiry and to the FDA and that the FDA in turn has a responsibility to the American public to approve the application that will permit mifepristone to be manufactured, distributed, and made available for indicated therapeutic purposes because of the overwhelmingly credible objective data that establishes it as a safe and effective drug.

In conclusion, I just wanted to say how pleased I was that Cynthia Person was able to introduce into your discussions the fact that mifepristone has a half life which is very short. In all of the discussions about the long-term complications that might come out of mifepristone's administration half life takes care of that problem.

DR. CORFMAN: The next speaker is Dr. Donna Harrison of the Southwestern Medical Clinic.

Agenda Item: Southwestern Medical Clinic - Donna J. Harrison, M.D.

DR. HARRISON: Dr. Davidson and members of the

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Advisory Panel, good afternoon. I am Dr. Donna Harrison. I am a board-certified obstetrician-gynecologist in private practice in Michigan. I have been invited here by National Right to Life. I have no financial interest in RU 486.

As a physician and as a woman I am concerned about the premature approval of RU 486 without requiring normal safety and efficacy testing. I have followed the RU 486-approval process for several years. Along with many other physicians, scientists, and members of Congress, I participated in the citizens' petition filed with the Food and Drug Administration last year.

This petition summarized the world's literature on RU 486 and clearly outlines the following main concerns: Number one, the up to 10 percent hemorrhage rate necessitating hospitalizations and emergency surgery, of which 1 percent will be severe enough to require blood transfusion. If only one-third of the 1.5 million abortions annually in the U.S. are converted to chemical abortions, that would still result in 5,000 American women hospitalized each year for hemorrhaging, 500 of these each year massive enough to require blood transfusion. This excess morbidity is completely unnecessary in light of the already available surgical abortion which has a fraction of this risk.

Number two, the 5 to 10 percent rate of pelvic

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infection requiring antibiotic treatment after chemical abortion with one World Health Organization study showing infection in a third of the women with incomplete abortions. In the U.S. if only one-third of the mean abortions annually were chemical, this would mean 25,000 American women with pelvic infections each year and a dramatic increase in subsequent sterility.

Number three, the 1 to 4 percent continuing pregnancy rate. There is also additional risk of severely deformed fetuses if the woman does not complete the entire procedure. In the U.S. experience documents poor compliance with 13 to 30 percent of surgical abortion patients failing to show for follow-up. In terms of RU 486 in real American women, this would mean 650 to 6,000 undetected pregnancies each year from failed RU 486 abortions. Who is going to assume the liability and cost of caring for these deformed children?

Note that the best results are from the French experience conducted under very tight governmental control with use only at or less than seven weeks from the last menstrual period as documented by ultrasound.

The Population Council has set up the popular expectation that RU 486 will be available with minimal medical supervision. That irresponsible communication undermines the need for tight medical control and clearly

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increases the risk of hemorrhage, infection, and undetected pregnancies in American women.

If we ignore the documented immediate risks, we : still left with the unknown and unstudied but predictable effects of RU 486 on other progesterone-sensitive tissues. Relying on six months of trials with follow-up of two weeks is inadequate to answer our concerns of the effects of RU 486 on the brain, the endocrine system, the breast, the ovary, and developing eggs and the immune system. All of these can be profoundly affected by progesterone and all of these contain progesterone receptors which could be bound by RU 486.

What of the pharmacokinetic data? What about the half life of RU 486 plus misoprostol? Where does RU 486 accumulate and with what effect? What is the combined effect of RU 486 and misoprostol? What is the effect of repeat usage. Note that 42 percent of abortions in the U.S. are repeat. Are we going to confine the use of RU 486 to once only? What are the effects of RU 486 with common medical problems. Testing and use has been confined to health women, but the Population Council has set up the popular expectation that this will be used by teenagers and women with poor access to medical care, many of whom are my patients. I deal with a 30 percent Medicaid population, and 20 percent of my patients have no private insurance.

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These are women with poor access to medical care who do not get appropriate medical screening.

What are the reasons for the discrepant results in minority populations, for example, Asian women with increased risk of hemorrhage? That will be the effect of a progesterone-mediated depression of the immune system on a growing HIV-positive population and the effect of RU 486 on a woman's chances of acquiring HIV?

The American public and the medical community do trust you to critically and impartially review RU 486 alone and in combination as an abortifacient. As a physician and as a woman I would urge you to prevent American women from being used as guinea pigs to satisfy a particular political agenda. Thank you for considering and addressing these grave concerns.

DR. CORFMAN: The next speaker is Joanne Hustead, the Women's Legal Defense Fund.

Agenda Item: Women's Legal Defense Fund - Joanne . Hustead

DR. HUSTEAD: Congratulations on making it through the afternoon. My name is Joanne Hustead. I am an attorney and the Deputy Director of the Women's Health Program at the Women's Legal Defense Fund. Established 25 years ago, the Women's Legal Defense Fund is a national profit advocacy organization that works on behalf of

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1 women and their families improving access to quality,
2 affordable health care including full reproductive choice
3 which is one of our key program areas. We appreciate the
4 opportunity to present comments today. We have no
5 financial interest in this product or any other conflict of
6 interest that would have any bearing on our comments.
7 We urge the Advisory Committee to recommend
8 approval of mifepristone as a means for the interruption of
9 early pregnancy. The record on its safety and
10 effectiveness is clear and compelling. It offers women an
11 essential alternative to surgical abortion for which
12 providers are increasingly scarce and simple access
13 increasingly burdensome and traumatic. Moreover, it may
14 have important applications in other areas as well.
15 This breakthrough drug has been trapped in a
16 political debate that has nothing to do with science, with
17 medicine or with the real needs of women and their
18 families. We are asking you to set mifepristone free and
19 to confirm the rational scientific basis of the American
20 drug approval process.
21 This drug combination would give women an
22 essential alternative to surgical abortion. A woman could
23 actually choose between significantly different medically
24 proven methods to find the approach that was most
25 appropriate for her. Making this drug combination

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1 available would expand and improve women's reproductive
2 health options in unique ways. One notable feature which
3 has been mentioned by other speakers is that it enables
4 women to terminate a pregnancy earlier than is sometimes
5 the case with surgical abortion. Because it could
6 potentially be administered in any doctor's office, it
7 could significantly ease some of the barriers that now
8 impede women's access to abortion in this country.
9 A stunning 84 percent of counties in the U.S.
10 have no abortion provider and the number of doctors trained
11 to perform surgical abortion continues to decline. The
12 medical education community's efforts to ensure that
13 doctors are trained in providing abortion services have
14 been stymied by Congress. Among trained doctors,
15 disincentives to providing surgical abortion include
16 threats to their personal safety and the safety of their
17 families. Those opposed to women's constitutional right to
18 choose are easily able to identify and target doctors who
19 perform surgical abortions.
20 Although there will always be a need for
21 providers of surgical abortion, training to induce abortion
22 with mifepristone would be different and easier. It is
23 reasonable to conclude that many doctors who do not now
24 provide surgical abortion services would include this drug
25 in their practices.

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Women seeking surgical abortion services face not only the challenge of simply locating a provider but also the likelihood of aggressive public harassment and the threat of violence at reproductive health clinics and medical offices. Approving mifepristone would help allow a very private and personal decision to remain as one.

This is a medical milestone with broad-ranging implications for women's health and ultimately men's health as well. Unfortunately, politics have artificially limited treatment options for all Americans. Denying or further delaying access to such important medical advances puts American women and men at an unnecessary and potentially tragic disadvantage.

In closing, you heard overwhelming testimony today that this drug combination is safe and effective. It is an appropriate and urgently needed alternative for women. Let us not deny women this safe and significant option. We urge you to recommend its approval. The women of America deserve no less.

DR. DAVIDSON: Now, that concludes the open public hearing. On behalf of the Committee, I certainly would like to thank all of the presenters who provided comments, opinions, and data in the consideration of the issues today. I am especially grateful that the time limitations that were set out in the beginning were so well

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pected and conformed to.

We will recess and reconvene in 15 minutes to continue the committee's deliberations.

[Brief recess.]

Agenda Item: Committee Discussion and Consideration of the Questions

DR. DAVIDSON: I want to do a couple of things before approaching the questions. The first has to do with resolving maybe this technical issue that has been raised about alcohol and smoking. First, my concern about alcohol was not that it was included as an exclusion in the clinical trials; but the patients were informed that they should neither smoke nor drink alcohol during the 48 hours following mifepristone administration and on the day of misoprostol, and that that was not a consideration in the patient information or the labeling. There are also some instructions about avoiding aspirin or any of its derivatives, steroidal or nonsteroidal anti-inflammatory drugs, prostaglandin synthesis inhibiting drugs, enzyme inducing drugs, oxytocic or prostaglandin, other than the one in the protocol. These were outside of the exclusions but were advisories to the patient.

With regard to smoking -- and Dr. Robbins, I understand, is prepared to respond to this -- as listed in protocol, 35 years of age and smoking seem to be

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separate exclusions in the French studies. I understand that Dr. Robbins may have a response to that and some other comments before we go further into the discussion.

DR. ROBBINS: Thank you, Dr. Davidson. I would just like to clarify a couple of things about the inclusion/exclusion, as you have already alluded to. In both the U.S. trial as well as the two pivotal French trials, the exclusion criteria was a combination of the following. Women could not -- women were excluded if they were 35 years or older and they smoked more than 10 cigarettes a day. It was a combination of the two in both protocols from France as well as the U.S. In one of those protocols the English translation as we have provided it had two separate bullet points for smoking and for 35. That has caused some of the confusion from the first protocol. In both of them when you read them in French the way they are written in French it is the combination as in our U.S. combination 35 years or older or smoking 10 cigarettes or more a day. And --

[Laughter.]

The other thing I wanted to speak to was a question that came up and Dr. Rarick said that the sponsor might have something to say about it. When Dr. Bardin had presented the cases of serious adverse events, as we always do, we presented that from the entire group that we had out

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to 63 days or less. However, of those 52 patients who were reported with the serious adverse events nine of those were 49 days or less of gestation -- so nine of the 52. Of those one of those of the four that had a transfusion was less than 49 days, and three of the 26 hospitalizations occurred in subjects that were less than 49 days just to give you that breakdown of the safety data.

Finally, the third point I would just like to clarify. The question came up about the issue of taking misoprostol specifically 36 to 48 hours later. As Dr. Spitz has said, from a pharmacokinetic point of view, that is the time when it is most sensitive. However, as the protocol states, you take mifepristone on day one and on day three you take the misoprostol. So you have the whole time on day three to take it. It is not strictly to the 48 hours in terms of the way the protocol as well as the labeling is stated. Thanks for letting us clear that up

DR. DAVIDSON: Okay. Does the committee have any questions?

DR. LEWIS: Actually, I would like to raise one question. We heard from one of the speakers, I guess it was Dr. Harrison about a World Health Organization study and some safety points that seemed to be different than what was found in the French pivotal study. I wonder if

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anyone has those data for our review or summary?

DR. DAVIDSON: I do not know if this answers this question, but this will be one shot at it.

. Paul Van Loek, from the World Health Organization, was invited here by the Food and Drug Administration -- by the Population Council, I am sorry. Thank you for correcting me on that. He, as I understand it, has had considerable experience with the international use of this drug. I would like to give him just a few minutes to provide some background in terms of his relationship to this drug experience and whether or not he has any particular comments that would be of benefit to the committee in view of some of the issues that have been raised today. If you could, if you could use the podium?

DR. VAN LOEK: Thank you very much for giving me the opportunity to talk. I am Paul Van Loek. I am the Associate Director of the Human Reproduction Program at the World Health Organization. This is a program that conducts research in reproductive health. It is a program that has been involved with research in mifepristone since 1982. We have conducted with this drug close to 50 different studies including several large multi-center trials on the use of this compound for induction of first trimester abortion, menstrual regulation, second trimester abortion, and cervical ripening. We have in these trials used different

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prostaglandins. We have used different treatment regimens of mifepristone, and we have done, as we always do, conducted these trials in a variety of developed and developing country settings. I should say right at the beginning that in the course of this experience we did not find any difference in efficacy or safety between different population groups. There was a question raised about that earlier whether data from the European women might be applicable to the different minorities here in the United States or of American Women in general. Certainly from the experience of doing trials in five continents we would not expect such a difference to occur.

During the course of the proceedings I have been flipping to the final data analysis of a most recent study that we have conducted in WHO with a protocol that is very similar to the French studies in terms of the timing of the misoprostol and the dose of the misoprostol. It is remarkable how similar the findings are to the data from the French studies as well as the preliminary data form the U.S. trial.

For example, if we look at efficacy -- and I have data -- the way that we did it was that the women were enrolled in the trial depending on the delay after the expected menstrual period. So, if we look at women with a lay of up to two weeks that would basically correspond to

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six weeks amenorrhea, the efficacy is 95.5 percent. Those between two and three weeks it is 93.2 percent. Similarly, in the case of serious side effects in this particular study, the incidence of emergency D&C because of heavy bleeding was 1.4 percent which puts it sort of half way between the one percent reported from France and the two percent from the U.S. experience. Similarly for blood transfusion. We find similar data as reported from France in the sense that the incidence is 0.2 percent. I was confused earlier when a mention was made that heavy bleeding occurred in 10 percent of the women. I do not quite understand how that was defined.

These are some of the main observations that I wanted to make, but I am open for any questions that the committee may have.

DR. DAVIDSON: Dr. Henderson?

DR. HENDERSON: In the WHO studies in developing countries, I gather that there really was not perceived by the investigators to be any problem with the three-visit requirement?

DR. VAN LOEK: No. And certainly that is the way that it is also being done now in China. China, of course, as you may know, or as I am sure you know, is the only developing country at the moment where the drug was being manufactured as well as being used on a wide scale in a

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slightly different regimen and is being --

DR. HENDERSON: What is the regimen?

DR. VAN LOEK: There are two regimens being used. One is a single 200 milligram dose. The other regimen is repeated doses of 25 milligrams given at 12 hour intervals.

DR. HENDERSON: What happens with a single 200-milligram dose?

DR. VAN LOEK: The same efficacy.

DR. HENDERSON: And they do not get followed up for a second visit?

DR. VAN LOEK: Yes. Of course, they have the similar routine scheme of three visits because they also have to come back for their prostaglandin.

DR. HENDERSON: And they do come back? In the developing countries they come back for that?

DR. VAN LOEK: That does not seem to be a problem. It certainly has not been a problem in our studies either. But, of course, we are talking here about women who make the choice to have this particular approach to pregnancy termination. So they know beforehand that this is what is going to be required. I guess, if someone has a difficulty in coming back for a second visit to get prostaglandin in a follow-up visit, then they may not opt for this regimen.

DR. HENDERSON: Do you have any data on the

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numbers that are lost to follow-up in developing countries?

DR. VAN LOEK: In general, but again, these are clinical trials so one should not consider these hard and fast data. In fact, it may be larger. But our follow-up rates or loss to follow-up rates rather have been less than two to three percent. Now, that means people not coming back for their visit number three. They generally come back for the prostaglandin.

The fact that they do not come back is generally taken that probably it was successful. It has been very different from center to center. In this particular trial, for example, two-thirds of the people who did not come back for follow-up came from two centers, Tunis, and the other one was Ho Chi Minh City.

DR. DAVIDSON: Dr. Lewis?

DR. LEWIS: Do you have any information about fetal effects in women who carried the pregnancy after failure?

DR. VAN LOEK: We have -- none of the women that we know carried the pregnancy to term. They all had their pregnancies terminated.

DR. DAVIDSON: Thank you very much.

DR. KOSASA: I have one question.

DR. DAVIDSON: Oh, I am sorry.

DR. KOSASA: We had heard about pelvic

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lammatory disease with the WHO studies. Could you comment on that?

DR. VAN LOEK: I do not quite exactly know which study was being referred to. My recollection of what was said was that 30 percent of women with incomplete abortion had pelvic inflammatory disease. Now that is a slight twist I think of what the actual paper may have said in the sense that, first of all, incomplete abortions will only represent two or three percent of the women in total. So 30 percent of those two or three percent is less than one percent. Without exactly knowing the paper my guess is from our experience that women who have an incomplete abortion and if there is some suggestion that maybe there is a degree of endometritis, they may get antibiotics perhaps just as a primary prevention. In fact I am quite sure that these were not confirmed clinical pelvic inflammatory diseases.

DR. DAVIDSON: Did I miss anybody else's question?

DR. NARRIGAN: I would like to ask for your overall view of this regimen. Do you think the benefits from the World Health Organization's perspective, outweigh the risks or problems?

DR. VAN LOEK: As I am sure you are aware, there about 50 million abortions in the world. Twenty

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1 million of those are done under unsafe conditions. Our
2 most recent estimates indicate that about 85,000 women die
3 as a result of unsafe abortions, and 50 -- all of those are
4 in developing countries.
5 There are a number of large developing countries
6 where abortion is being provided on fairly broad liberal
7 ground so to speak. The two that spring to mind are China
8 and India. Together they account, of course, for something
9 like 2.2 billion people. Both of these countries, China
10 less than India, have some difficulty in providing safe
11 surgical abortion services partly because of the need to
12 have skilled people able to do it. If you can have a
13 method that will remove some of the strain on surgical
14 abortion services that would be an advantage. We saw
15 this -- we mean the World Health Organization -- we saw
16 this method as a potential benefit in those circumstances.
17 That is why the World Health Organization became involved
18 in studies of this kind. Clearly, these two countries
19 themselves have taken the decision that this is indeed
20 something that will be of benefit to them because China is
21 producing it and using it and India I understand is about
22 to start producing it as well.
23 DR. O'SULLIVAN: I have one last question.
24 Knowing full well how studies are conducted in terms of
25 follow-up and so on, can you tell me if in the studies

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1 conducted by the World Health Organization there were
2 efforts to get patients back in to make sure that they came
3 in or whether they are just given the medication with an
4 appointment to come back in and relied upon to come back
5 in?
6 DR. VAN LOEK: No. Generally speaking in all of
7 our studies, if people do not turn up for the follow-up
8 visit, then the staff will go out and try to find them.
9 With abortion it is sometimes a bit difficult because, for
10 all sorts of social reasons, people may not always live at
11 the address that they give to the staff.
12 DR. O'SULLIVAN: Oh, yes. We know that.
13 DR. DAVIDSON: Any other questions?
14 [No response.]
15 Thank you.
16 Before addressing the questions, do any of the
17 members of the committee have any other general questions,
18 concerns or observations to make before?
19 DR. AZZIZ: I have a question that maybe somebody
20 from the Population Council can answer. It may be obtuse.
21 We are really essentially considering a regimen not just a
22 single drug at this particular point, which is a little
23 unusual. The recommendation right now is 48 hours later
24 for the delivery of misoprostol. The question is what if
25 that drug were delivered four days later or five days

later? Would it be totally ineffective? Do we have any data in that regard? The reason I am asking that is most of the side effects of this regimen, if not all of them, are really related to the prostaglandin which is not being under consideration for approval and not to the mifepristone which is. So perhaps somebody from the Population Council could answer that.

DR. BARDIN: That is an important question because, as you already heard, the effectiveness or the synergism between the two drugs begins to be lost beginning about 48 hours after the first drug, the mifepristone. The protocol that was done in the U.S. study said that the patients should receive the dose on the third day, which is the second visit, anytime during that day. It allowed the clinician, however, to administer the drug if the patient did not come back but they came back the next day or the next. That allowed the physician the option to administer the drug that day if the patient came in because any number of things could delay the patient coming in. So we will have the opportunity in the U.S. study to examine that possibility. So that will be available to the FDA and to the prescribing physicians.

DR. DAVIDSON: Someone for the agency might be able to clear this up. My understanding, however, would be that we would have to stick to the recommended protocol.

Are there any other general -- yes?

DR. HENDERSON: I am very concerned that we are considering this regimen for a highly-selected and motivated population. I asked earlier in the U.S. study, the clinical trials, was there any demographic information we could look at understanding that the analysis is not completed, but at least to give a sense as to at some point in the near future we would be able to look at the breakdown of the patients who were being followed who have received this regimen?

DR. DAVIDSON: Is that a question, a comment or a hope?

DR. HENDERSON: Well, it was a comment of a question that I had asked earlier.

DR. DAVIDSON: Sure.

DR. HENDERSON: I was told that we could see the demographic data with the understanding that it is not analyzed but just to see the racial, the economic breakdown of the patients who were in the U.S. trial. I was told that was available.

DR. WINIKOFF: One of the issues is that the drug is so effective that there is very little difference between any subgroups that we have looked at. It is extremely effective in all of the subgroups. But, if you look at it, we have approximately one-third non-Caucasian

patients. The effectiveness -- what?

DR. HENDERSON: But the non-Caucasian -- there are Asian, there are Hispanics, there are African-Americans.

DR. WINIKOFF: They are all represented. I do not remember, but the proportions are approximately equal, but they are not far from that. They are all represented. As a result, no one group is very large. They are a little less than a third of the total.

DR. HENDERSON: So that is about a thousand patients who were divided in many ethnic groups?

DR. WINIKOFF: Yes. But some people claim more than one ethnicity, also.

DR. HENDERSON: Okay.

DR. WINIKOFF: We have a really diverse population. Even with 2,000 people you do not get very big cells if you start dividing it up a lot. We certainly have to give it --

DR. HENDERSON: And insurance coverage or socioeconomic status?

DR. WINIKOFF: The only indicator of socioeconomic status was payment. We have a small subgroup that only covered their medical care with Medicaid payment, but that was under a hundred patients.

DR. HENDERSON: And adolescents?

DR. WINIKOFF: No one under 18 was admitted to the trial because of informed consent issues.

DR. O'SULLIVAN: How about totally non-paying ingredients -- non-insured, non-paying?

DR. WINIKOFF: There were non-insured. There were some non-insured.

DR. O'SULLIVAN: What approximately?

DR. WINIKOFF: They are listed as self-pay because we do not know whether they could afford to self-pay or they could not afford to self-pay. But if they needed to pay they would have to self-pay.

DR. O'SULLIVAN: Well, what I am talking about is to make it very easy. Illegal aliens, migrant workers, that group of patients that --

DR. WINIKOFF: We did not, as far as we know, did not have any illegal aliens, but we did not ask people whether they were illegal aliens.

DR. O'SULLIVAN: So you do not know?

DR. WINIKOFF: Of course we also have age and parity issues which are part of the demographic profile that you might want to look at. The geography is spread out across the United States. So in terms of representation by region we have that as well.

DR. HENDERSON: Well, actually, I am not so concerned about age and parity. I am concerned about

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patients who cannot afford -- access. That is what I am really interested in.

DR. WINIKOFF: In terms of the effectiveness of drug?

DR. HENDERSON: No. In terms of following up for three visits, and ethnic issues, access to care, transportation, child care issues that will prevent them from being followed up for the second and third visit. That is what I am interested in.

DR. DAVIDSON: Does it help if they know up-front that those visits are required?

DR. HENDERSON: I do not think so. Because I think if women desperately want it then they will figure out that they will do something when they are faced with that issue. But right now they want the drug. What happens when they cannot show up for the second and third visit or when they cannot afford to have the termination because it has failed, the surgical procedure? I mean, what do we do with those populations of adolescents, of minority women who are already lacking access to pregnancy termination?

DR. DAVIDSON: Let me ask -- I understand. What general assurance do you have in listing patients for these protocols that they will follow through with any scenario whether it is surgical termination or otherwise?

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DR. WINIKOFF: Let me say something first about studies in general. The most important thing in the study is to find out whether the drug is safe and effective. So our highest priority is to get complete records on all patients. So, in that sense, you may say that the situation is somewhat artificial, irrespective of ethnicity. Dr. Van Loek mentioned that in the WHO studies people go out to find patients because it is extremely important to know what happened. What we found out is that with complete follow-up there are very few patients who need extra care or who do not complete the abortion. So we are at least assured that problematic outcomes are relatively rare.

Now, how the drug operates when it is offered in real life as it were is always different and it always needs to be looked at after it is offered in real life. You cannot get answers to real life questions in study circumstances. So I think that your concern is valid but it is one that needs to be addressed as a product is used and as it is available. It cannot be addressed in a study situation. But we have some reassurance because we have such a safe and effective drug.

DR. O'SULLIVAN: I think you have to address one part of it, and that is that, if this were to be approved, n what is going to have to be looked at somehow or

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another and dealt with is what do you do for the patient who completes her course but cannot afford the surgical termination. How do you follow-up a patient or patients who start out the therapy and, for reasons which women will change their minds about many things in life, suddenly decide it did not work to quote what I often here, this was God's will, I am going to keep on with the pregnancy? How do we follow those up? I mean, this is probably post-marketing surveillance. But I think that it is essential that if we were to approve this that post-marketing surveillance of this type has to be done.

DR. WINIKOFF: I agree that we in all medical care have issues like this. There is no reason to suppose that the surgical abortion would not be part of the package the way the cesarian is part of the package of obstetrical care. If you run into a complication that requires a more complicated delivery, it is part of the service. If you run into a complication that requires a curettage, it is part of the service. So surgical patients also need reaspiration sometimes and they also get it as part of the service. So I think that these things are medical care issues that our system is already dealing with. I agree that they are very important.

I think a lot of the issues are not so far into providers of abortion. Surgical abortion patients also

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sometimes cannot afford care and run into complications and need to come back at a later point. And the system has accommodated that and can continue to accommodate that. It obviously is something --

DR. DAVIDSON: Dr. Daling?

DR. NEWHALL: May I respond to that? I just have a couple of issues. The women that we generally serve in our downtown women's center clinic generally are of lower economic status. Women with good health insurance much more often will avail themselves of services in a private offices. So we already serve the lower socioeconomic women primarily.

Number two, as Beverly said, the price includes whatever surgical back-up is necessary. You pay one price, and you end your pregnancy. I think that it is important to remember that women are motivated to have a complete, and safe, and effective abortion. They come to us because they want to have their pregnancies terminated. They are motivated to complete the process and they are motivated to have their health care adequately protected. We put Laminaria in women for surgical abortion and they always come back. We have a very high follow-up rate in our clinic. Women are interested in preserving their good health. They do come back. Now, there are occasional circumstances when they cannot. They call up, they say how

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ey are doing, and they come back at a later time. But
e women who did this trial with us understood that there
re two drugs that worked together and that the first step
pened on Monday, and the second step happened on
dnesday, and it was not a one-stop shopping -- that they
solutely needed to come back Wednesday or there was
solutely no guarantee that their abortion would be in
fect. So all of the women came back for the second visit
d there were very few who did not come back for the third
sit. In fact, what we did was we saw a lot of women
ur, five, and six times just because we were all in the
arning process. We encouraged women to come back more
ten rather than less often. We saw a lot of our women.
am very comfortable that they all received good, adequate
alth care and were very comfortable coming back as often
they needed to for the questions they had and the
rvice that they needed.

DR. DALING: In this trial did the women pay for
eir abortions?

DR. ROBBINS: No, they did not.

DR. DALING: Were they given financial
mpensation?

DR. ROBBINS: No.

DR. DALING: I heard this morning -- I asked the
estion about follow-up and I heard that there was a

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dred percent follow-up for all three visits. And I
oke to you a little while ago and you said, well, that
is not true that for the third visit you had three women
o did not return. You just had 172 in your group or
mething to that effect. I guess that I am a little
ncerned that these numbers -- the hundred percent follow-
) is not really an accurate figure.

DR. NEWHALL: There were some women who I think
id not actually physically come back to the clinic but
ey were contacted by phone and they were not bleeding,
id they had had nonviable pregnancies before they left, so
t was not really a question of -- there were no ongoing
regnancies or any ongoing health problems.

DR. DAVIDSON: Dr. Zones, did you have a
uestion?

DR. ZONES: It was just answered.

DR. DAVIDSON: Oh, okay. These are important
uestions, however, in bits and pieces we are drifting into
me questions that are already on our list. So, if the
mmittee is comfortable, why don't we start with the
uestions? Are there any objections to that?

[No response.]

Agenda Item: Discussion and Response to
estions

DR. DAVIDSON: Let's read the first one. The

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1 regimen proposed for the use of mifepristone for the
2 termination of early pregnancy consists of the oral
3 administration of 600 milligrams of mifepristone within 49
4 days after the beginning of the last menstrual period,
5 followed by oral administration of 400 micrograms of
6 misoprostol 48 hours later.
7 I have one question about that 48 hours that I
8 would like to ask both the agency or the Population
9 Council. All of the clinical data in general relates to a
10 window of 36 to 48 hours rather than this specific 48
11 hours. Is this an issue that should be modified now or
12 should it be left as it is?
13 DR. RARICK: Are you proposing to say 36 to 48
14 hours or are you proposing to say two days? Which one are
15 you talking about?
16 DR. DAVIDSON: I am asking -- that is the nature
17 of my question. Since you have specifically 48 hours --
18 DR. RARICK: No. We say the regimen proposed.
19 And that is draft labeling proposed by the Population
20 Council. If you feel that we need to recommend a different
21 36 to 48 or two days, as it is stated in the patient
22 labeling, we could certainly take that under advisement and
23 you could change that section to what you are comfortable
24 with.
25 DR. DAVIDSON: Well, let me ask, in regards to

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1 two days versus 36 to 48 hours, people who are familiar
2 with the trials, is that -- which one of those would be
3 more accurate in terms of what is clinically being
4 requested?
5 DR. ROBBINS: Two days.
6 DR. DAVIDSON: Two days. And that falls within
7 the window of effectiveness and synergy that is true?
8 PARTICIPANT: Two days later.
9 DR. DAVIDSON: What is your question?
10 DR. RARICK: I think that is what the patient
11 labeling says, anyway. So I am sure you are comfortable
12 with that.
13 DR. DAVIDSON: Okay. So we are changing this to
14 two days. Is that acceptable to the committee?
15 PARTICIPANT: That is better.
16 DR. DAVIDSON: That is better I hear. Okay. All
17 right. I think that we will have less problems if it is
18 stated that way. So you understand the proposed regimen
19 and it has been modified so that the misoprostol will be
20 administered two days later rather than 48 hours.
21 Question 1A. Do the results of the open label
22 historically controlled studies conducted in France
23 establish the efficacy of this regimen for use in the
24 United States? Any discussion or questions on question
25 one?

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[No response.]
Are you ready to vote on question one without any further discussion?
DR. O'SULLIVAN: No.
[Laughter.]
I am just thinking about it. I think that I would like to say that with a caveat that it would have been preferable to have U.S. data. In fact, we are talking about the fact that everybody is quoting that this has been used in 150,000 women throughout the world and yet the data presented is something like one to two percent who were ever studied at least that we have data on and that data is not even American data.
DR. DAVIDSON: But the question restricts this in a way that you can either respond or object to. The question limits it to the French.
DR. O'SULLIVAN: Okay.
DR. DAVIDSON: Any further discussion of this question?
[No response.]
Do the results of the open label historically-controlled studies conducted in France establish the efficacy of this regimen for use in the United States? Are there any further questions?
[No response.]

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Let's take the voting members. All in favor of that statement, raise your hands.
PARTICIPANT: You mean yes to that statement?
DR. DAVIDSON: Yes. Yes to that statement, raise your hand.
[Show of hands.]
One, two, three, four, five, six.
Opposed?
[Show of hands.]
Six to two. Yes, I have counted myself.
PARTICIPANT: So it is six to two?
DR. DAVIDSON: Yes. If not, what additional efficacy information should the applicant provide? Yes?
DR. HENDERSON: I think a less-selective patient population. These are highly-motivated women who were selected and had their terminations paid for by the clinical trials. I think that it should be women who are much more likely to avail themselves of the services in the states.
DR. DAVIDSON: I am going to --
PARTICIPANT: I am going to use the formal minority report and put it on the table so that --
DR. DAVIDSON: Well, let me tell you -- let me explain where I think I am here. The committee by a majority vote supports the first question that the French

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data is sufficient for efficacy. The second was an if not question; but since there were two people objecting what I am hoping to provide at least for the record as to what those objections are. So it would be helpful if you would clarify if that fits into this scheme here what those objections or further conditions should be in regard to the French data.
DR. O'SULLIVAN: In regards to the French data?
DR. DAVIDSON: Well, that is what the question is.
DR. O'SULLIVAN: What additional efficacy?
DR. DAVIDSON: Yes.
DR. O'SULLIVAN: It does not say that it has to be from the French data.
DR. DAVIDSON: Well, either way you would like to respond.
DR. O'SULLIVAN: I would like to see the final American data. I agree with Cassandra that it is very much of a study situation. I think it would be wise if we could see what would happen in what I would call the main stream of Americans who would be going to do this I think like she did.
DR. DAVIDSON: I am sure that both of you -- just a comment -- are familiar with the fact that study populations are always somewhat special and that

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translation from that to a non --
DR. HENDERSON: Yes, but the patients who were not going to come back are a patient population that is very, very different. If necessary, then they need to be studied separately in a separate study. I commend the Population Council for bringing this to the FDA. I think it is a very valuable tool for taking care of women and increasing reproductive rights and options, but I also believe that there is a great risk for harming a very large, vulnerable population if we do not study them and make sure that once this is available that they are not irreparably harmed.
DR. DAVIDSON: Is that sufficient?
DR. O'SULLIVAN: I agree.
DR. DAVIDSON: Those are two points. Yes?
DR. AZZIZ: I am not a voting member right now. I just wanted to add a comment.
DR. DAVIDSON: But you have no restrictions to speak.
DR. AZZIZ: And I will take that. I have the same concerns as far as requiring -- I am not as concerned about the population data. I mean, populations that are noncompliant will be noncompliant with everything from surgical terminations to ectopic precautions. But I am concerned that in a fairly sensitive environment that we

are in we do not have the complete U.S. efficacy data which is promptly available but not today. I would like to make a comment that perhaps for this type of situation that would be very ideal.

DR. DAVIDSON: Would it be acceptable to advise the agency that when the U.S. data is available, if there is any significant difference than the French data that we would at least like to have an opportunity to review that? Would that be an unreasonable -- I understand what you are saying because, if the U.S. data comes in and there is essentially no significant difference in any respect than at least to the point that data is available to answer that question it would be reviewed. And, if there are differences, then since the committee has been invited to advice up to this point, then perhaps we would be interested in seeing it. What does the committee feel about that?

DR. LEWIS: Agreed.

DR. HENDERSON: I am off the committee.

[Laughter.]

DR. DAVIDSON: The committee is an institution that goes on.

[Laughter.]

DR. HENDERSON: Okay.

DR. DAVIDSON: So whatever the concern is it is a

committee concern that is institutionalized. All right.

The committee -- you may want to -- the committee has reservations about final efficacy questions without the U.S. data and recommends to the agency that if this data when completed is significantly different than the French data that the committee would like an opportunity to review it. All in favor of that, raise your hand.

[There was a show of hands and the motion was approved unanimously.]

That is unanimous.

DR. HARRIGAN: Mr. Chairman? You mean worse than? If it is better than, it is moot.

[Laughter.]

If it is better than --

DR. DAVIDSON: Do you want -- what would you -- if it is worse than? Is that acceptable, if it is worse than? Okay. Thank you very much. Worse than. We might want to see it if it is better.

PARTICIPANT: Yes.

DR. DAVIDSON: Okay. Is that all right?

PARTICIPANT: Sure.

DR. DAVIDSON: The second question. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience. A, do these data adequately

demonstrate that the regimen is safe for use in the United States when use for the proposed indication? I do not think -- okay, Dr. Sullivan?

DR. O'SULLIVAN: What foreign postmarketing experience did we see?

DR. PETITTI: This was a question that I asked actually Dr. Rarick about the postmarketing surveillance experience and adverse stress experience from the British Committee on Safety of Medicines and other drug regulatory agencies, and I was reassured by her that that information had been reviewed and that it did not present an adverse event profile different from what we saw from the trials from France and the United States. Is that a correct summary of your and Dr. Bennett's summaries?

DR. RARICK: What I said was that the Population Council had submitted a report about post-marketing surveillance to their I&D and asked them if they wanted to comment on it. In my recollection there was not anything of startling or unexpected findings in that report.

DR. PETITTI: We did hear comments on cases of acute myocardial infarction and other kinds of adverse cardiovascular events associated with the regimen of mifepristone and misoprostol, and it was my understanding that that was part of the international adverse drug experience. Am I correct?

DR. RARICK: Correct.

DR. DAVIDSON: Okay. Do you have all of the information available that you would like? Let me read it again. The safety database for the regimen consists of trials conducted in France, preliminary data from U.S. trials, and foreign post-marketing experience. Questions. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? In your discussion please include comments on the following issues whether the adverse events associated with the regimen can be adequately managed when the regimen is administered as labeled, the acceptability of the frequency of adverse events? Any discussion on this question? Yes?

DR. PETITTI: I would like to comment that safety is a relative term and that although this may be safe for this indication, I think that some of the information that I have seen in the popular press and some of the rhetoric surrounding this regimen and this drug leads people to think that safe is equivalent to free of adverse effects. I am impressed in the data that have been presented here that although the frequency of adverse effects is low that there is a significant and important number and frequency of adverse effects and that this needs to be carefully understood by the consumer and by providers who might seek

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to deliver this service. So I want to worry that the term safe not be misinterpreted as free of adverse effects and free of actually serious adverse effects.

DR. DAVIDSON: Good. But then are you remarking in the vein that that is a labeling and a patient information leaflet problem?

DR. PETITTI: But an important one.

DR. DAVIDSON: Yes. Okay. All right.

DR. DALING: Ezra, I would like to see some collection of multiple procedures for an individual women, I mean, not in regard to our decision here, but I think that that is something that information needs to be collected on.

DR. DAVIDSON: Could that be done in number 7?

DR. DALING: Yes.

PARTICIPANT: Number 7.

DR. DAVIDSON: Okay. Then we have a rich opportunity to raise all of those kinds of questions. Okay. Let's read it again and see where we are and how you feel about it. The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials and foreign post-marketing experience. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? You have discussed the adverse emphasis and

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that needs to be taken as a high and clear priority in terms of labeling and patient information leaflet. Are you ready to answer that question? Any unreadiness?

[No response.]

All in favor or who support that raise your hands.

[Show of hands.]

Seven.

Any opposition? Abstention?

DR. O'SULLIVAN: Abstain.

PARTICIPANT: She is abstaining.

DR. DAVIDSON: Abstain. Seven for and one abstention.

Would the second bullet, the acceptability of frequency of adverse events, do you have anymore to say about that other than points that may ultimately be raised as labeling or patient information leaflets?

DR. LEWIS: I think acceptability should be perhaps looked at compared to what, compared to other methods of pregnancy termination, compared to carrying a pregnancy? Acceptable depends on -- it is a relative term. I think that it should be couched as such.

DR. DAVIDSON: Is it -- this is a question to the staff, to the agency -- is it possible, or are there data I guess we do have data on alternative --

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DR. KESSLER: One way to think about that question is what a rational person and a rational physician talking together, knowing all of the adverse events both known and unknown would be acceptable -- would that risk be acceptable for a rational person? Would they want knowing those adverse events to possibly avail themselves of the drug? That is a way to think about that.

DR. DAVIDSON: Okay.

DR. LEWIS: Well, it is not so much the way of thinking about it I suppose as a way of answering the question or -- I mean, to just say flat out yes sounds a little ridiculous because it is not that simple a question. But I think if you say, well, it compares favorably with surgical methods of pregnancy termination then that seems to be --

DR. KESSLER: It certainly is another way to answer that question.

DR. LEWIS: Something like that.

DR. DAVIDSON: So your interest would be to the extent that it is possible --

DR. LEWIS: Uh-huh.

DR. DAVIDSON: -- that the method be compared with alternatives in terms of adverse effects and events?

DR. LEWIS: Yes.

DR. DAVIDSON: And you would like to include that

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as a comment to the agency in the labeling to the extent that that is possible?

DR. LEWIS: Yes.

DR. DAVIDSON: I think that is a very good point and may be very helpful in terms of perspective.

DR. LEWIS: Yes.

DR. DAVIDSON: Since you have answered A in the affirmative, I guess there is no necessity for B if not, but I will give you an opportunity anyway, knowing this --

DR. LEWIS: We are never at a loss for words.

DR. DAVIDSON: Dr. Azziz?

DR. AZZIZ: I will take the opportunity again to echo the same thing. I would like to see the finalized U.S. data on safety. In fact, I am not sure that I would favor it being sent only if it is different. I would rather I think have it sent --

DR. DAVIDSON: You mean only if it is worse.

DR. AZZIZ: But no, in this case, I think that the safety issue should be reviewed when it is finalized period as opposed to --

DR. O'SULLIVAN: Better or worse?

DR. AZZIZ: Better or worse.

DR. O'SULLIVAN: For richer or poorer.

DR. AZZIZ: That is right. I would appreciate seeing the data either way is what I guess I am saying.

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That is my comment.

DR. DAVIDSON: Well, we could change the -- we originally said that and then we modified it to be worse.

DR. AZZIZ: I am not sure. There are only eight committee members. I think it perhaps would not be that much of a task to send the data anyway once it is finished regardless of what -- because you see it is a very subjective issue as to whether it is worse or better than France. It will not be identical. So I think that the members may find it useful to get that data.

DR. DAVIDSON: Do you want to comment on that -- interpret that movement?

DR. RARICK: I said, no, I do not want to comment.

[Laughter.]

But, no, but I think we have heard you that you are very interested in seeing the results of the U.S. study probably either way. You are simply very -- you are appropriately curious as to the final result.

DR. CORFMAN: I think it would be good for the committee to know whether we are likely to bring data back too.

DR. RARICK: As a group in a public setting?

DR. CORFMAN: Uh-huh.

DR. RARICK: I think we would have to think about

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it depending on the results. If they are the same or better they may get to receive them simply in the mail with an opportunity to comment. If they are appreciably worse, then maybe they will -- I cannot really answer that question.

DR. DAVIDSON: Okay. All right.

Are we ready to go to three? Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe that the benefits outweigh the risks for the use of the regimen for the proposed indication in the United States?

DR. O'SULLIVAN: Can I ask a question?

DR. DAVIDSON: Sure.

DR. O'SULLIVAN: Benefit to whom?

DR. DAVIDSON: Do you want to answer that question?

DR. RARICK: The regimen is proposed for use for woman for the termination of pregnancy for a woman to take.

DR. O'SULLIVAN: Because, if you are talking about a woman, it may be a benefit to her, but it is certainly of no benefit to her baby whatsoever.

DR. DAVIDSON: Well, the benefit is to the woman.

DR. RARICK: It is proposed to be taken by the man to terminate the pregnancy.

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DR. DAVIDSON: Okay. Let's read it again to make sure. Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States which is to complete an abortion?

DR. HENDERSON: I would like to add to it a select population of well-motivated, highly-motivated women. I think that you cannot -- I cannot comment on the whole population across all socioeconomic statuses and the availability of access to health care. I think that is a very limiting part of our society.

DR. DAVIDSON: Well, are you saying that it should read informed and well-motivated or other than that? You want to add informed and well-motivated?

DR. HENDERSON: Yes. That may be difficult. Just leave it and I will just add my comment. You can leave it.

DR. DAVIDSON: Leave it as it is or do you want it modified?

DR. HENDERSON: No. I will just comment. Leave it.

DR. DAVIDSON: Any other comments? Are there any other comments as to how this question is worded?

DR. O'SULLIVAN: I want to know what the exact

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wording of this is going to be.

DR. DAVIDSON: We will do that.

DR. NARRIGAN: I just wanted to respond to Cassandra's concerns. I am much more reassured having heard even informal comments from the WHO representative concerning it seems to me the safety in very, very complex situations. It is not the United States I understand.

DR. HENDERSON: The WHO went and got patients, and they went and visited them. They called them if they did not come. Most of the women that I am concerned about, no one is going to go and get them. No one is going to call them because a lot of them do not have phones. Those are the women that I am concerned about.

DR. LEWIS: That is always the case in a clinical trial though. I mean, anybody conducting a clinical trial has a responsibility to follow up with their patients.

DR. HENDERSON: Right. That is why I --

DR. LEWIS: And you are not going to get data until after it is approved in a non-ideal population. I just think that it is not going to happen.

DR. DAVIDSON: We are generating a fair amount of response to this.

DR. DALING: Maybe we can work on this in question seven, post-labeling surveillance.

DR. LEWIS: You could qualify it.

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DR. DAVIDSON: Would that satisfy you? Look at seven?

DR. HENDERSON: I looked at seven. It is ...stmarketing.

DR. DAVIDSON: I mean, would your concerns be accommodated if there were appropriate conditions raised in regard to question seven?

DR. HENDERSON: I will think about that.

DR. DAVIDSON: Okay. Dr. Zones?

DR. ZONES: I have a couple of thoughts. One is that this is an additional option for women seeking to terminate pregnancy. Therefore, they can weigh the cost and benefits of each of the methods and which was best for them through the advice of their physician. But also it seems to me that there are other medical procedures where we face the same difficulty. The one that comes to my mind is cervical dysplasia where, if the physician thinks that the woman will not continue to seek care, they will do a much more invasive procedure than if they think the person is likely to come back. It seems to me in this situation that physicians or providers will have to make judgments about what is the most appropriate procedure in consultation with the patient.

DR. DAVIDSON: Yes.

DR. DALING: One other comment. A lot of these

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...udies were carried out in Planned Parenthood. I think that they see a population, a broad population, and one -- a population that has a high concentration of the type of people whom I think Cassandra is concerned about.

DR. DAVIDSON: Any further comments? Did you have one?

DR. AZZIZ: No. Actually, that exactly was my point. I think that it is true that there is some bias because they have been paid to come back.

PARTICIPANT: Well, they are not paid.

[Discussion off record.]

DR. AZZIZ: Well, let me rephrase that. Their expenses have been covered. Okay. Wait a minute.

PARTICIPANT: Free care? They are provided free care?

DR. AZZIZ: Weren't there termination --

PARTICIPANT: Their procedures were paid for.

DR. AZZIZ: The procedure was paid for.

PARTICIPANT: It was free.

DR. AZZIZ: Well, let's not get into semantics. The procedure -- let me just finish a comment here.

PARTICIPANT: They had access.

DR. AZZIZ: There is some bias because obviously these people were highly sought for and their termination ...penses were covered; however, I just simply wanted to

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echo the fact that most of these patients were actually indigent patients who do attend planned parenthood and other clinics and, thus, represent a more difficult sector of the population. So I am not quite sure that I agree with Dr. Henderson's comments that this represents a significant bias.

DR. DAVIDSON: As a generic observation though in clinical research regardless of what the issue is, there is always a concern that once you move from clinical trials which has a selective focus on it, what is going to be the compliance and other questions when it is put in general?

DR. HENDERSON: I understand that. The thing that concerns me is that at the second visit, if they do not show up, what happens? They then come back with a pregnancy that has not been aborted that has been exposed to a new medication? It is not just simply that they are different, but the consequences are so dire that they may have a fetus that they are forced with having to decide to terminate because they have been exposed to this medication. They may be coerced into having a suction because they delayed the prostaglandin. I understand that all clinical trials when you put them into practice are going to be different.

I just think the consequences of this particular trial if women do not follow-up are so severe that it just

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requires extra caution besides just knowing that it is going to be different in practice. Because I think that the potential for coercion, the potential for adverse perinatal outcome I think is great. I just think that that needs to be addressed because it is not just simply putting a clinical trial. If it was one drug and they did not show up and you deal with the consequences, that is fine; but there are two drugs, and you need to confirm that the pregnancy has been avoided. And there are all kinds of consequences -- there is a mechanism that just sets off a cascade that if they do not follow through is so severe that I think it is different than just any clinical trial.

DR. KOSASA: Dr. Davidson? We have kind of run into the same problem with Laminaria. We put a Laminaria in and then if the patient does not come back we get quite nervous and try to find them.

DR. HENDERSON: I understand. But then you do not have -- you have this concern that maybe she is going to have a preterm delivery. You have the concern that maybe she is going to have an infection. But you then do not have the concern that she carries a fetus that may have some malformations. And while we have the data that suggests that it is highly unlikely, if she does, it will be highly unlikely and difficult to prove that it was not something that we did and gave it to her. I think it is

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very different. I mean, I agree with you. Laminaria is a problem when you send patients home and ask them to come back. But I think the consequences are so vastly different that it concerns me.

DR. DAVIDSON: We have been told by some of the people who are working with the populations that include at least some patients in the category that you are concerned about that compliance seems to be reasonable. I guess that is not enough to satisfy what your reservations are. However, do you accept -- this is really a question -- that some of your concern and reservation is also hypothetical?

DR. HENDERSON: Absolutely.

DR. DAVIDSON: Okay. Let's read the question again and see where we are.

Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for use of the regimen for the proposed indication in the United States? Is there any further discussion or comment on readiness about voting on that question?

[No response.]

If not, may we vote?

If yes, raise your hands.

[Show of hands.]

That is six, am I right?

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PARTICIPANT: Are you voting?

DR. DAVIDSON: Yes, I am voting. Raise your hands. Six. All right.

Opposed?

[Show of hands.]

Abstentions?

[Show of hands.]

Six yes, two abstentions.

PARTICIPANT: No, one -- which are you doing the voting no or abstaining?

The voting, yes.

PARTICIPANT: Let's do it again, please.

PARTICIPANT: I am sorry.

DR. DAVIDSON: Okay. All yes, raise your hands.

[Show of hands.]

One, two, three, four, five six. There are two abstentions.

PARTICIPANT: I thought it was seven.

DR. DAVIDSON: No. Only eight people voted.

PARTICIPANT: Why don't you let us finish, Cindy?

PARTICIPANT: It is six.

DR. DAVIDSON: It is six.

PARTICIPANT: Six. And how many are against?

DR. DAVIDSON: Two abstentions.

PARTICIPANT: Two abstentions. Thank you.

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PARTICIPANT: Who is voting?

PARTICIPANT: Deborah and Mary Jo.

DR. DAVIDSON: There are eight votes.

PARTICIPANT: I think it is a generic question as to who is voting at this table.

DR. RARICK: The voting members include Dr. Daling, Dr. Henderson --

DR. DAVIDSON: There are eight voting members.

DR. RARICK: -- Dr. Petitti, Dr. Davidson, Dr. O'Sullivan, Dr. Marrigan, Dr. Lewis, and Dr. Kosasa. There are eight.

DR. DAVIDSON: Right. Okay? Next question. If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients to receive it to be appropriate?

DR. DALING: I think they need to add to the labeling that the studies done to date do not apply to women who are over 35 and are smokers or smoke more than 10 cigarettes per day since the data was not collected on those people.

DR. RARICK: Do you have any specific concerns about that age group or smoking-specific concerns that you think they are at higher risk for some reason? I just wanted to --

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DR. DALING: They may be. I mean, they certainly must have been thought to be because they were eliminated from this study to begin with.

DR. DAVIDSON: The group that was eliminated, if I understand this, are the ones who are over 35 and smoke?

DR. DALING: That is right.

DR. DAVIDSON: That is what you are saying?

DR. DALING: That is what I am saying.

DR. DAVIDSON: Over 35 and smoke. And what is your question now?

DR. RARICK: Some of the medical conditions such as prior cardiovascular disease were not included in the proposed labeling, yet again they were eliminated from the studies.

DR. DALING: They were included in the provider labeling but not in the patient labeling.

DR. ZONES: Were there contraindications?

DR. DAVIDSON: Your interest is that the conditions that were excluded in the trial should also be identified as exclusions in the patient -- at least that the trials did not include patients with those conditions?

DR. DALING: That is right. Just that information. We do not --

DR. DAVIDSON: Just provide that information.

DR. DALING: We cannot really address that issue.

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DR. DAVIDSON: Okay. Do you understand that? In regard to labeling the concern is that the conditions and cautions in the clinical trial protocols should be provided as information in the patient information leaflet, such as chronic conditions and over 35 and smoking -- those have not been tested.

DR. HENDERSON: I think adolescents also have not been tested.

DR. O'SULLIVAN: There are a couple of other things that I would like to bring up. Some of them are wording issues and labeling that I had some difficulty with or the way it should perhaps -- may own peculiarities.

DR. DAVIDSON: This is the time to bring them up.

DR. O'SULLIVAN: Yes, well, there are quite a few. I do not know if you want to go through all of them.

DR. RARICK: Are you suggesting specific wording?

DR. O'SULLIVAN: Yes.

DR. RARICK: If you have a general concept that you would like us to work on or if you could give us a draft of your -- I mean, if it is a general --

DR. O'SULLIVAN: I could give you the draft, yes.

DR. RARICK: Are there any specific issues you would want the committee to agree or not agree on?

DR. O'SULLIVAN: Well, two things. I think that under contraindications I have some concerns about things

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like cardiac disease and insulin-dependent diabetics. I mean, there is no information regarding those entities. Obviously, these are entities that women might consider this procedure for.

DR. DAVIDSON: I think that is close to the objection -- the question that is being raised already. That should be included in the patient information.

DR. RARICK: Those of you with specific editing or wording suggestions, we would appreciate simply letting us have those suggestions so that we could take that under advisement. In this meeting, we would like you to think of expressing just sort of the general concept as Mary Jo and others have that you are concerned that the exclusion criteria somehow be reflected. We could then take that under advisement.

DR. DAVIDSON: At least the front part of her question is similar to the first advisory. You had others?

DR. O'SULLIVAN: Under the section where it talks about drug interactions and it says that in addition, drugs known to cause enzyme induction -- I am not quite sure I understand what that means. I think that that needs to be a little bit more specific.

DR. DAVIDSON: Okay.

DR. O'SULLIVAN: I have a lot that I would like to leave with Phil. But I guess I think that some of the

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wording even in terms of the patient's part of that -- are we dealing with that too now?

DR. DAVIDSON: Yes.

DR. O'SULLIVAN: Even in terms of the patient's part of that, I was trying to read this both as a patient and as a physician. I think that there are things in here that ought to be worded differently.

DR. DAVIDSON: Well, actually, the patient part is number five.

DR. O'SULLIVAN: I could leave my comments with Phil.

DR. DAVIDSON: But, if you have any other generic ones that are more than just editing, then I think they ought to be raised.

DR. O'SULLIVAN: Yes, there is one other one. Under -- this is page 10. It says visit day three, the third paragraph under that. It says because of the risk of malformation of the embryo as a result of the treatment procedure patients who have an ongoing pregnancy at visit three must be prepared to have it terminated. But there is no information whatsoever about what the risk of malformation would be. I think that in order for somebody to be able to make a decision here about must be terminated, they ought to have some idea of what information, if any, is available. It should be in there.

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DR. PETITTI: I had a similar comment on page 2 where there is a discussion of the teratogenicity studies. In fact, I think it should probably be made a little stronger in relationship to the embryo toxicity studies. It seems to me that the data from misoprostol strongly support the conclusion that it is a teratogen and that that is the reason for recommending that a pregnancy that continues after exposure to both mifepristone, misoprostol be terminated based on a probabilistic assessment that you cannot rule out the possibility of a congenital defect after that exposure. I think that it is a little weak the way it is written now and that is a generic comment both for the patient and the physician labeling.

DR. O'SULLIVAN: I do not think that we have the information to say that it is a teratogen.

DR. PETITTI: I think the animal data supports the conclusion that it is a teratogen. It is a pregnancy class D drug when given -- class X drug when given for its other indication.

DR. RARICK: It is X, right?

DR. PETITTI: X.

DR. O'SULLIVAN: But it is an X because there is absolutely not enough information. The only animal data we have is in rabbits -- the rats and rabbits. The monkeys -- I mean, there is very little of anything really except in

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some rabbits.

DR. PETITTI: I think there is data from humans to suggest that it is also teratogenic in humans.

DR. RARICK: Excuse me. I think the misoprostol labeling that you are referring to -- is that what you are referring to?

DR. PETITTI: Yes, I am referring to misoprostol.

DR. RARICK: It has a boxed warning not to be used in pregnant women, but it is because it causes abortion, not because it is a teratogen. It is not a class X drug.

DR. PETITTI: That is a good clarification. I think I tried to ask that question.

DR. RARICK: And the data from Brazil on its use is not -- support the teratogenic.

DR. KESSLER: Why don't we -- and I know it is late -- Dr. Jordan, why don't you just go to the microphone, if you would? It is a very important point. The teratogenicity of misoprostol in laboratory animals -- what is on the labeling and what is known?

DR. JORDAN: Okay. On the labeling it says that it is not a teratogen for misoprostol; however, there are other data for other PGEl's that show that there is a possibility that it is a teratogen in rats, but I have not reviewed specifically that data. It is kind of new data.

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't for misoprostol itself it says that it is not a teratogen.

DR. DAVIDSON: Unless you have captured this otherwise I think, and I want to repeat this for the committee, that regarding labeling for the physician and patient is that the committee is concerned that the cautions, and the conditions, and exclusions that were in the clinical trial protocol for information should also be included in the labeling and the patient information leaflet saying that there is no data as to what the effects would be with these associated conditions. Okay? And the recommendation for pregnancy termination should be worded in a way that it is an unknown specific risk but there is a risk. Since it is unknown, it is advisable that pregnancy termination occur if there is failure. I am restating that to see if that is what the committee is concerned about.

DR. O'SULLIVAN: I would say that it should it be considered, but would not say advisable.

DR. DAVIDSON: Well, say to be considered.

DR. HENDERSON: Or offered.

DR. DAVIDSON: Offered. In other words, they are seen as to be less demanding. Okay.

Are there any other concerns about questions four? Since we have talked about five these are labeling d informed consent questions. Are there any additional

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concerns about four and/or five?

DR. AZZIZ: I have a concern with the section on dosage and administration. Under visit two day three of misoprostol administration there should be a comment there stating that, again, for information to the physician, the provider that the effectiveness of the misoprostol administration may decrease with a greater delay in its administration or its timing. We do not really know whether given three days later or four days later it is still or not effective. I think we should simply note there that the effectiveness of that may decrease.

DR. DAVIDSON: That emphasizes that point of the two-day dose.

DR. AZZIZ: Correct. But for the practitioner I think it is important to understand why that issue needs to be given that way. Because there is nothing here to indicate that that may become less effective.

DR. O'SULLIVAN: Why even select two days?

DR. AZZIZ: Yes. Why two days? I mean --

DR. DAVIDSON: Well, they said some of the synergy --

DR. AZZIZ: I understand that, but there is nothing in the physician label.

DR. DAVIDSON: Okay. It should be included in the labeling as to why there is that two-day limitation.

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Okay. Anything else?

DR. ZONES: I alluded to this before, but I wanted clarification. In the provider labeling it lists chronic conditions about which there is very little information. I think that those should be itemized in the patient packaging.

DR. DAVIDSON: Yes, we said that.

DR. ZONES: Yes. Also, it says that you should report to your physician any drugs that you are taking. I think that you should list drugs, particularly aspirin and other common OTCs.

DR. DAVIDSON: Well, that is also included in the cautions and instructions that were in the clinical trial protocol.

DR. ZONES: I just want the patients to have the specific details because sometimes they catch stuff.

DR. DAVIDSON: We have requested that that be placed in both. Any other? Yes.

DR. PETITTI: I was myself on page six moderately confused about what one would do with the nursing mother. I think that this arises from the use of the regimen where misoprostol is not recommended for use by lactating women; but for mifepristone you have to decide whether or not to discontinue nursing or discontinue the drug. I think there is a contradiction there and it needs to be resolved.

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DR. DAVIDSON: So, in essence, the advice would be that the regimen would not be commended for nursing mothers rather than dividing it this way?

DR. HENDERSON: Do we know whether it is stored? I mean, why can't they discard that milk for the two or three days and continue nursing? Why do they have to stop nursing?

DR. PETITTI: I am only saying that misoprostol --

DR. HENDERSON: But if they do not nurse while they are taking -- if they do not give the baby the milk while they are taking the medication, why could they not resume nursing after the termination if they are still producing milk? I do not know. I mean, I am just asking if that is --

DR. PETITTI: I am only saying that given that misoprostol is not recommended and it does not explain why it is not recommended for nursing women that the advice should be the same.

DR. DAVIDSON: Can you comment on this, Dr. Rarick?

DR. RARICK: I think we hear you that potentially we could work with the sponsor on that section of the labeling to either have it be consistent not to use it in lactating women or to tell lactating women to stop

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tating during its use.

[Laughter.]

PARTICIPANT: Turn on and turn off?

DR. RARICK: Do you understand what I mean? Stop breast-feeding.

DR. DAVIDSON: Either way would work.

[Laughter.]

DR. RARICK: To add to Dr. Petitti, I think the warning in the misoprostol is an actual label because it is a chronic-use labeling. So we will have to work with this sponsor with how we work on that section. Thanks for pointing that out.

DR. O'SULLIVAN: While you are on that page, too -- and I wrote a note about this -- pediatric use. It says safety and effectiveness in pediatric patients. Well, what is a pediatric patient? I mean, if pediatricians -- the adolescents and the pediatricians will tell you up to age 23. So somehow we are going to have to deal with that.

DR. RARICK: Right. The sponsors probably are trying to conform to our pediatric use guideline document, and so we will have to work with them again on that.

DR. DAVIDSON: Let me ask a question about another issue. Are you through with the lactation?

Efficacy diminishes with gestation age. Is there appropriate emphasis as written that the decreasing

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efficacy, which is a success of what 91 to 92 percent if it is near 49 days versus 97 percent of so if it is much earlier? Is that difference significant enough that it should have higher emphasis in the patient information leaflet? What about the people who conducted these studies?

DR. O'SULLIVAN: According to the data the drop-off is after 49 days.

DR. DAVIDSON: So that is not significant enough to be of any concern?

DR. BARDIN: It is a highly statistically significant observation; however, it does not make a lot of clinical difference as long as you stay below 49 days.

DR. DAVIDSON: Okay. All right.

DR. BARDIN: So I think that both statements are correct.

DR. DAVIDSON: Well, then we do not need to bother.

Are there any other comments or concerns in regard to four and five having to do with labeling and the patient information?

DR. NARRIGAN: I have just an unfortunate procedural -- I did not receive this document so I am going to abstain because I have not had a chance to review it.

DR. DAVIDSON: But this -- we are not going to

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vote on these two. We are just raising issues.

DR. NARRIGAN: The labeling?

DR. DAVIDSON: Right.

DR. NARRIGAN: Oh, I am sorry. Okay. Thank you. I misunderstood.

DR. DAVIDSON: Well, let me read the question and see if we are responding. If the regimen were to be approved do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who are receiving it to be appropriate? We are providing a lot of comments that have taken -- so we did not vote on it being approved. Is it necessary since we are giving you all of this other advice? So whatever -- but if you have any -- even in your present reading, if you have any questions or concerns, this would be the opportunity to raise them. Okay.

DR. RARICK: I think you are safe to answer the rest of the questions as commentary probably. Instead of voting and then commenting you might as well just give us the actual --

DR. DAVIDSON: Well, we were kind of going in that -- we tried to as much as possible do what we are instructed and requested.

[Laughter.]

Does someone have -- yes?

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DR. PETITTI: I have just two other relatively minor comments — well, one minor, and one major. I think that physician or the labeling should say written informed nsent rather than informed consent. I think that most hysicians are used to informed consent, but this is ctually a specific requirement for written informed onsent.

On the actual patient consent form where there is the part where people are going to be asked to sign, I ould like to have something perhaps added that the hysician has discussed alternatives — just maybe a entence: "My physician has discussed with me alternatives o medical abortion, including surgical abortion, ontinuation of the pregnancy." I wonder if perhaps since ometimes patients actually read these things and pay a lot f attention to them that there might be a statement that ould say my doctor has confirmed that I am pregnant and hat the pregnancy has not lasted for more than 49 days, or omething that affirms that that patient sort of nderstands what the doctor told her.

DR. DAVIDSON: Okay. I think that that is a good oint.

Any others in regard to four and five?

[No response.]

If not, are you ready to move to the next number

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x? If the regimen were to be approved do you have ecommendations concerning the drug distribution system roposed by the applicant? Now, that has to do with only a hysician, the training involving pregnancy, dating, ctopic pregnancy identification and surgical evacuation of he uterus and the dispensation would be in the doctor's ffice or clinic. The drug would be provided directly to he provider.

DR. O'SULLIVAN: Again, I have a question.

DR. DAVIDSON: Yes?

DR. O'SULLIVAN: There are nurses who do bortions who are recognized to be able to do that. Are hey countermanded from the opportunity to do this as part f the abortion services that they provide?

DR. DAVIDSON: Would someone from the Council ike to answer that in terms of what intentions are?

DR. WINIKOFF: Use of the drug the way it is roposed has to be under the supervision of a qualified ysician.

DR. O'SULLIVAN: So under the supervision? That s fine.

DR. DAVIDSON: That is what I thought. Yes.

DR. O'SULLIVAN: That is fine.

DR. DAVIDSON: Okay.

DR. AZZIZ: A point of interest, I think, for

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information, I mean, those nurses have to have physician supervision at some level.

DR. O'SULLIVAN: I believe they are supposed to, yes.

DR. AZZIZ: So that would cover that.

DR. O'SULLIVAN: Well, I just wanted to make sure.

DR. DAVIDSON: Okay. All right. Are there any other questions about the proposed distribution system?

DR. O'SULLIVAN: The other question I have is how — this recordkeeping that the physician is going to have to do — that is exactly the same as the IUD record system? Is that exactly what you are proposing? It would be no different from the IUD recordkeeping system?

DR. WINIKOFF: It is precisely modeled on the IUD system. I think that in all of the largest elements it is the same. I cannot tell you that the actual forms are the same.

DR. O'SULLIVAN: My point is that it should be a simple as possible because in today's world with all of this stuff that doctors have to do in the office plus how fast they have to do it and how quickly they have to turn it over, and the amount of paperwork that they have to do it is getting to the point where you do more paperwork than you do patient work. It has got to be simplistic.

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DR. WINIKOFF: I certainly appreciate that. I am sure that we do not want to encumber the physicians who are using the drug.

DR. O'SULLIVAN: It will stymie them from using it at all.

DR. DAVIDSON: All right. Are there any other suggestions or comments about six?

DR. RARICK: I would like some clarification. I am assuming that this would be distributed to any provider who requested it. But would there be some way of validating it?

DR. DAVIDSON: There were training and skill —

DR. RARICK: That was what I was wondering. How is that being evaluated?

DR. HENDERSON: Well, it would be like the Norplant system, I assume.

DR. RARICK: I have not heard that.

DR. DAVIDSON: How would physician and provider selection be operationalized?

DR. HENDERSON: Thank you. That is much better wording.

[Laughter.]

DR. WINIKOFF: The distributor will be the entity responsible for operationalizing the actual training of the physicians.

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DR. HENDERSON: Who would?
DR. WINIKOFF: The distributor of the drug.
DR. HENDERSON: Meaning you?
DR. WINIKOFF: No. We are not the distributor.
DR. HENDERSON: Oh, I see.
DR. RARICK: Who is? As far as the validation that the physicians have appropriate training, the physicians will have to certify that they do. But there is proposed to have an examination of the physicians.
DR. ALLEN: My name is Dr. Susan Allen. I am the President of Advances in Health Technology. I am very pleased to be here today. My responsibility and the responsibilities of my organization will be to ensure that providers are trained and that the qualifications that you have heard discussed earlier today are met. Only physicians who have had training in how to administer the drug, how it works, what the side effects are, what the complications are, and how to manage those side effects and complications will be able to order and receive the drug.
DR. O'SULLIVAN: And how will you supervise that they have had experience in giving it?
DR. ALLEN: We will basically ensure that they have received that training. We are not going to go in and supervise every physician and watch them do it.
DR. O'SULLIVAN: That is what I am trying to

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erstand. You are going to bring physicians in to see at they know how to give the patient a pill?
DR. ALLEN: No. We are going to provide training for physicians throughout the country to ensure that they do know how the drug works, what it is about, how well it works, what the side effects are, and what the complications are, et cetera. But we are not going into every physician's office and watching them administer pills to women.
DR. O'SULLIVAN: Let me try it another way. Are you going to have meetings and seminars?
DR. ALLEN: Yes. We will be doing seminars throughout the United States.
DR. O'SULLIVAN: Well, now I have another question. If you are going to do these seminars, are you paying the physician to come to the seminar?
DR. ALLEN: No. We are not going to be paying the physician to come.
DR. O'SULLIVAN: I just wanted to make sure.
DR. RARICK: Dr. Allen, I think the question also is, okay, now you are going to be providing to those physicians only? Do you have to have records on them that they self-identify that they are trained?
DR. ALLEN: Yes. We will know which physicians indeed been through the training program, yes.

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DR. RARICK: Not just the training program, but they self-identify that they have training in surgical technique, that they have training in diagnosing an ectopic pregnancy, that they have training in the diagnosis of gestation. Those are some of the -- the provider requirements will be self-identified.
DR. ALLEN: Yes. We will ask them those questions. If you also recall when you go through medical school you learn how to date a pregnancy. You learn how to diagnose --
DR. O'SULLIVAN: No, no, no. That does not work that way.
DR. ALLEN: I disagree, but okay.
DR. DAVIDSON: I just want to caution you that you are looking at a table full of professors here.
DR. ALLEN: I know. I do respect that.
[Laughter.]
DR. KESSLER: Can I just ask on one point? In the slide that the Population Council showed it took careful introduction and distribution requirements. One of these things is physicians who have had training and then it listed three things. Is that only your training or does a board -- let's start with a board-certified obstetrician who has --
DR. ALLEN: Right.

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DR. KESSLER: They do not have to take your training.
DR. ALLEN: That is right.
DR. KESSLER: They have to be able to certify that they have met this. But you will also offer training and then physicians can certify?
DR. ALLEN: The way that the training will be done -- it will be done in two phases. The first phase will be in providers who currently make surgical abortion services available so they already have those skills.
The second phase of training will be done in clinicians who do not currently make surgical abortion services available. And that will include training in manual vacuum aspiration. So there will be a component ensuring that physicians who do not right now provide surgical abortion services have some training in manual vacuum aspiration.
DR. AZZIZ: I have a comment. I think we are treading on very dangerous ground. One, we are trying to dictate medical practice which is not what we can do. Secondly, I think that it is an error and probably needs to be addressed now to train nonsurgeons to do a procedure which is a D&C on a pregnant uterus which is extremely risky.
Now, early on I asked the question whether the

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same physician who administered mifepristone had to do the D&C if there was a failure? The answer was no. He or she had to have backup for that. So before you all get into p water by training family practitioners who have never done surgical procedures to do a procedure that is complicated, I would simply readdress the issue. Do these physicians simply need to identify a backup surgeon in the event of a five percent failure rate in which case then the issue is resolved? I would like you to address that clearly because we are getting conflicting information.

DR. ALLEN: Well, first of all, I do think that it would be important for physicians who do not right now make surgical abortion services available to indeed identify clinicians who could provide backup services for them. I am not an OBGYN physician. I provided thousands of abortions in the United States and was trained in approximately two weeks time to perform instrumental evacuation of the uterus. I do not think it is necessarily appropriate to say that family practitioners, pediatricians, internists, et cetera, will not be able to make evacuation of the uterus a safe procedure. I think that it can be done.

DR. AZZIZ: My concern is that I would not tie this drug which we are considering to the training which is rather radical. I mean, you are a highly-motivated, very

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elligent person who wants to do this. That cannot be translated to a large population of physicians. So I would not tie what you just recommended to this drug approval process because I think that is wrong to do so.

DR. ALLEN: Point well taken. But I also do not think that -- every physician in this country is not going to want to make this drug available to women; but there will be many who do and they will want to acquire the skills that are appropriate to manage the side effects and complications.

DR. LEWIS: I have to agree with Dr. Azziz. I do not think you can teach somebody to do a surgical evacuation of the uterus in a simple seminar with a mannequin or something.

DR. HENDERSON: I think you can. You just cannot handle the complications.

DR. LEWIS: No. And you are talking about something that you would have to do in only five percent so you would do this actually infrequently in contrast to yourself. It is not that the person is a family practitioner or an intern, it is also the frequency with which they do those procedures. So, if you are talking bout in an emergency situation having the skill to be able o do this deftly, appropriately, and with minimal plication, such a person who has never been trained in

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that and who has only attended a seminar is the worst possible choice of person to do that. They should have a surgeon available as backup.

DR. ALLEN: Again, point well-taken. I think the other thing when I mentioned that there would be two phases of training, the two phases will also be very different. The first phase of training in which you have providers who currently make surgical abortion available will have to be much less intensive because they already have the skills. When you talk about the second phase of training, and you are taking on not just a didactic session but a practicum session as well, it is not something that will probably be able to be done in a day. It may take a few days. It may take observation and participation by those particular clinicians in a clinic that right now makes those surgical abortion services available.

DR. AZZIZ: Again, I am confused. Your training of nonsurgeons to do procedures surgically in two weeks' time is a radical and I think very interesting approach. Is this what the committee is being asked to look at or not? Because originally we never thought this was. I think this is why I am concerned that this is getting involved. We are simply going to ask physicians to identify a backup if they do not do the procedures at this point.

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DR. ALLEN: This is not to my understanding a part of the labeling that you will be reviewing. I do not think that you are being asked to approve that.

DR. DAVIDSON: But we are being asked to comment on the distribution system. This is part of what is being proposed.

DR. KESSLER: And it is our understanding that the distribution system will be a part of the labeling.

DR. RARICK: Essentially.

DR. DAVIDSON: Right. I think what you are hearing from the committee as the issue of skills being discussed, there is considerable unease about how that certification and documentation is going to be done to ensure safe delivery of this regimen and management of its complications.

DR. ALLEN: Point taken.

DR. DAVIDSON: I think that it is a comment that the committee is just --

DR. RARICK: Let me ask the question a different way, Dr. Davidson. Does the committee agree with the concept that the distribution system of provider certification providing only to providers who are certified and that they have training in blah-blah, and blah, is that something that you can live with as the restricted distribution system -- that we will work further as to how

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that is going to be verified, confirmed, or is there anything else you would want to add?

DR. DAVIDSON: We may want to take a vote on that whether or not that we agree in concept with the proposed distribution but we have some serious reservations about how it is currently described in terms of assuring safe and adequate credentialling.

DR. AZZIZ: But just to bring it back again. The labeling currently proposed does not bring in any of these concerns that we have just been sprung on.

DR. DAVIDSON: That is the reason why -- so would you want to vote on what I have just said that we agree in concept with the proposed distribution but we have serious concerns about how certification of the skills is presently described?

DR. RARICK: I do not think that you need to vote on that, Dr. Davidson.

DR. DAVIDSON: We do not?

DR. RARICK: I think we hear that comment.

DR. DAVIDSON: Oh, okay.

DR. RARICK: If everybody agrees?

DR. DAVIDSON: So you just took a vote.

DR. RARICK: I am sorry.

[Laughter.]

DR. RARICK: You can go right ahead and vote.

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[Laughter.]

DR. DAVIDSON: Well, since we voted, anyway, all in favor of that, raise your hands.

[There was a show of hands and the motion was approved unanimously.]

DR. DAVIDSON: Unanimous.

Finally, postmarketing.

DR. HENDERSON: I think the distribution system should be monitored postmarket -- in the postmarket study.

DR. DAVIDSON: The first suggestion is that the distribution system should be monitored postmarket.

[Laughter.]

DR. KESSLER: But, Dr. Henderson, you have a little conflicting recommendation. You want to keep records simple. Now, are you saying that every physician who administers this should be involved in postmarket surveillance and that is a requirement of participating?

DR. HENDERSON: I think we should monitor complications in the postmarket survey, that is surgical complications -- complications from failed terminations from the medical therapy. That is what I am most concerned about.

DR. KESSLER: Survey or 100 percent of every physician who participates?

DR. HENDERSON: Reporting surgical complications

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following this medical procedure.

DR. KESSLER: For every physician who participates?

DR. HENDERSON: Should report surgical complications.

DR. O'SULLIVAN: Could another way of asking that or another way of dealing with that be that those physicians who are already credentialed to do this either in hospital facilities, ambulatory care facilities, or by the departmental chairman would not have to do that, but those who are not credentialed in that manner would have to do that?

DR. DAVIDSON: That is one way. There are various ways to look at that distribution. Because in instances where there are already clinical privileges being monitored in this regard, there may be less of a need in terms of looking at the skill question.

DR. AZZIZ: Yes, just a comment again. I think you are right, Dr. Kessler. You do not want to make it over-burdening, but you do need some information. I think that segregating out as to whether it is a university doc or an OBGYN-certified would be unfair to our family practice internal medicine colleagues who we want to encourage to use the drug if it is approved.

I think a time-limited survey of six months, a

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year, two years, across-the-board, everybody using would be a much more useful thing. Because we may find out that family practice with a good OBGYN backup may do better than some OBGYNs who think that they can take care of everything. So these are issues that I think would be better just on a timeline survey, a year, six months, or whatever.

DR. O'SULLIVAN: You have also got to recognize one thing when you do that -- that the guy who is the backup will be also taking care of the complication of the other one. So this is something that I can tell you for board exams. So you know you examine candidates for boards and then you look at this big, huge list of complications, and you find out that this is the backup to two or three other people and he has the complications.

DR. KESSLER: Dr. Davidson, may I just ask -- we appreciate your advice. The sponsor is here. I was wondering whether the sponsor would be willing to commit generally to this kind of advice?

DR. ARNOLD: Yes. We are willing to discuss it.

DR. DAVIDSON: Oh.

DR. KESSLER: We take that as a yes.

[Laughter.]

DR. DAVIDSON: Are there any other post-marketing suggestions or concerns?

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[No response.]

A couple I have heard before and that is some way f looking at long-term probably following some xpopulation to look at long-term effects of both single nd multiple use would be helpful.

DR. DALING: I think we need to document how many omen actually come back for all three visits.

DR. HENDERSON: Incomplete treatment.

DR. DALING: For the three treatments, especially he second.

DR. DAVIDSON: All right.

DR. DALING: And what the loss to follow-up ctually is.

DR. DAVIDSON: Okay. The other is, as possible, he experience over age 35 --

DR. HENDERSON: Who smoke.

DR. DALING: And under 20.

DR. DAVIDSON: -- who smoke.

PARTICIPANT: Under 20?--

DR. DAVIDSON: Because although there are autions here, there clearly are people who both the hysician and the patient may accept this on certain risk n these categories. To the extent that it could be ocumented it would be helpful. Some of the clinics or et etera may have that. Okay.

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DR. AZZIZ: I think it will be very important to eep a record and maintain a record of pregnancies who have eceived mifepristone, for example, and continued it. ecause, clearly, we do need -- that will be a major uestion in three or four years and we need that.

DR. DAVIDSON: Okay. Anything else?

[No response.]

I do not have any other questions. So, if there s nothing else, are there any final comments or anything lse we need?

Oh, one thing. We have some committee members ho are departing. That was over the microphone.

[Laughter.]

We can do this quickly. Dr. Corfman has provided s with some certificates documenting your participation on he committee for Drs. Henderson, Daling, and Dr. Zones.

DR. ZONES: Thank you.

[Applause.]

DR. DAVIDSON: On that note, we will adjourn.

[Whereupon, the meeting was adjourned at 6:38 .m.]

Food and Drug Administration Establishment Inspection Report

Date Assigned: 01/24/2000 **Inspection Start Date:** 12/09/1999 **Inspection End Date:** 12/14/1999

Firm Name & Address: Mishell, Daniel R Md , 1240 N Mission Rd Rm 2k1 , Los Angeles,CA 90033 US

FEI: 2080597 **JD/TA:** 11 **County:** LOS ANGELES **Est Size:** [redacted]

Phone: (213)226-3104 **District:** LOS-DO **Profiled:** No

Conveyance Type: **% Interstate:** **Inspectional Responsibility:**

Endorsement

This inspection of a clinical investigator was conducted in response to a written assignment from HFD-46. This inspection requested a Clinical Investigator Data Audit Inspection of Dr. Daniel R. Mishell for Population Council NDA #20-687 for Mifepristone & Misoprostal Protocol #166A.

The previous inspection was conducted 6/96 and revealed minor record keeping errors and some deficiencies in the informed consent form.

This inspection revealed no major deficiencies. Records were much improved from the previous inspection although there were a few very minor deficiencies encountered. No FDA-483, Inspectional Observations, was issued to Dr. Mishell. This inspection of a clinical investigator was conducted in response to a written assignment from HFD-46. This inspection requested a Clinical Investigator Data Audit Inspection of Dr. Daniel R. Mishell for Population Council NDA #20-687 for Mifepristone & Misoprostal Protocol #166A.

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CLASSIFICATION: NAI - N/N

FOLLOW-UP: Upon Center Assignment

O: Los-Do
cc:HFD-46
cc:FMD-145
cs:Bimo Monitor - [redacted]

Endorsement Location: See below (FACTS)

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
[redacted]	01/24/2000 03:22 PM E		E

APPEARS THIS WAY
ON ORIGINAL

FEI:2080597 **Inspection Start Date:** 12/09/1999 **Inspection End Date:** 12/14/1999

Firm Name & Address: Mishell, Daniel R Md , 1240 N Mission Rd Rm 2k1 , Los Angeles,CA 90033 US

Related Firm FEI **Name & Addrress of Related Firm:**

Registration Type

There are no Registration Types

Registration Dates

Establishment Type

7 Clinical Investigator/Animal Clinical Investigator

Industry Code

60 Human Drugs

District Use Code:

0 zero

C TO BE EDITED

U TO BE EDITED

APPEARS THIS WAY
ON ORIGINAL

FEI: 2080597 **Inspection Start Date** 12/09/1999 **Inspection End Date:** 12/14/1999

Firm Name & Address: Mishell, Daniel R Md , 1240 N Mission Rd Rm 2k1 , Los Angeles,CA 90033 US

Inspection Basis: Compliance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/Process	Reschedule Inspection Date	Re-Inspection Priority	Inspection Conclusions
48811	Clinical Investigator/Animal Clinical Investigator	60			No Action Indicated (NAI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	01/24/2000	No Action Indicated (NAI)	[redacted]	LOS-PREAPP

Remarks:

APPEARS THIS WAY
ON ORIGINAL

FEI: 2080597 **Inspection Start Date:** 12/09/1999 **Inspection End Date:** 12/14/1999

Firm Name & Address: Mishell, Daniel R Md , 1240 N Mission Rd Rm 2k1 , Los Angeles,CA 90033 US

Products Covered

Product Code	Est Type	Description	Additional Product Description

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PA	Establishment Typ	Process	Hours
[redacted]	INV	LOS-DO	48811	Clinical Investigator/Ani	60	52
					otal Hours:	52

APPEARS THIS WAY
ON ORIGINAL

FEI: 2080597 **Inspection Start Date** 12/09/1999 **Inspection End Date:** 12/14/1999

Firm Name & Address: Mishell, Daniel R Md , 1240 N Mission Rd Rm 2k1 , Los Angeles,CA 90033 US

Inspection Result

EIR Location
Central Files

Trips Nu

Inspection Summar
This inspection of a clinical investigator was conducted in response to a written assignment from HFD-46. This inspection requested a Clinical Investigator Data Audit Inspection of Dr. Daniel R. Mishell for Population Council NDA #20-687 for Mifepristone & Misoprostal Protocol #166A.

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This inspection revealed no major deficiencies. Records were much improved from the previous inspection although there were a few very minor deficiencies encountered. No FDA-483, Inspectional Observations, was issued to Dr. Mishell.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

APPEARS THIS WAY
ON ORIGINAL

Refusals

Inspection Refusals: No refusal

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?: **483 Location:**

Response Type	Response Mode	Response Date	esponse Summary

APPEARS THIS WAY
ON ORIGINAL

Dr. Daniel R. Mishell
1240 North Mission Road, #2K1
Los Angeles, CA 90033
12/9-12/14/99
CFN: 20 80597

SUMMARY OF FINDINGS:

This inspection of a clinical investigator was conducted in response to a written assignment from HFD-46. This inspection requested a Clinical Investigator Data Audit Inspection of Dr. Daniel R. Mishell for Population Council NDA #20-687 for Mifepristone & Misoprostal Protocol #166A.

The previous inspection was conducted 6/96 and revealed minor record keeping errors and some deficiencies in the informed consent form.

This inspection revealed no major deficiencies. Records were much improved from the previous inspection although there were a few very minor deficiencies encountered. No FDA-483, Inspectional Observations, was issued to Dr. Mishell.

HISTORY OF BUSINESS:

Dr. Mishell is a practicing physician at Los Angeles County/University of Southern California Medical Center Women's and Children's Hospital located at 1240 North Mission Road, Room 2K1, Los Angeles, CA 90033.

The title of the study under investigation is "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol In Inducing Abortion in Pregnant Women With Amenorrhea of Up To 63 Days." Dr. Mishell enrolled 204 patients, completed 192, terminated 2 and had 10 lost to follow-up.

There were a number of sub-investigators associated with this site:

PERSON'S INTERVIEWED/INDIVIDUAL RESPONSIBILITY:

Credentials were shown and an FDA-482, Notice of Inspection, was issued to Nurse Manager Contraceptive Research. was present throughout the inspection and provided the majority of information for this report. was the coordinator for this study. Dr. Mishell was present briefly each day of the inspection and involved in the exit discussion. Dr. Mishell is the most responsible individual for this site and maintained control of all records associated with the study.

Dr. Daniel R. Mishell
1240 North Mission Road, #2K1
Los Angeles, CA 90033
12/9-12/14/99
CFN: 20 80597

INFORMATION REQUIRED BY THE PROGRAM:

SPECIAL INSTRUCTIONS:

This clinical investigator is not performing any studies for government agencies.

AUTHORITY AND ADMINISTRATION:

The investigator was informed of the status of the drug, nature of the protocol and obligations via the protocol, memos and meetings. Dr. Mishell retained control over and knowledge of the study.

PROTOCOL:

Copies of the protocol were available and provided. IRB approval was granted on 8-18-94. A revised informed consent was approved on 8-30-94 this is the informed consent that was used throughout the study although the IRB stamp still has the original date stamp of 8-18-94.

SUBJECTS RECORDS:

The investigators files were organized, complete and legible. There was adequate information in the files to assure that all subjects did exist during their participation in the study. 15 subjects files were reviewed. There did not appear to be any major discrepancies between the clinical investigators raw data and the case report forms completed for the sponsor. There were 10 patients who were lost to follow-up, but there were numerous documented attempts to contact these patients. Additionally, there were two patients who were terminated from the study. There were some minor deficiencies noted during review: Patient #073 was two weeks late for Visit #3 and her gestational age appears that it should be 41 days not 32 days. Patient #111 her gestational age was calculated wrong, Patient #142 her gestational age was calculated wrong, and Patient #168 one hour blood pressure and heart rate were not done on Visit #2. Dr. Mishell stated that he did understand the importance of clear and accurate records and that he would attempt to further improve their record keeping skills.

CONSENT OF HUMAN SUBJECTS:

The IRB approved consent forms were found in each of the subjects files. All consent forms appeared to have been signed prior to the subjects entry into the study. There were two consent forms approved for use in this study: One English language and one Spanish language. There was conditional approval granted on 8-18-94 with revised approval being granted on 8-30-94. The

IRB stamped all consent forms with a date of 8-18-94. Attached as Exhibit #1 are copies of both informed consent.

INSTITUTIONAL REVIEW BOARD:

The IRB is: [redacted] The Chairman of the IRB is [redacted] Dr. Mishell obtained approval for the study prior to enrolling any patients. There was a single advertisement which was approved for this study. The ad was approved on 9-13-94. A copy of the advertisement and approval are attached as Exhibit #2.

SPONSOR:

The investigator did provide copies of the IRB approved consent form to the sponsor. The sponsor contracted with [redacted] conducted numerous on-site visits as well as extensive correspondence with the investigator. Attached as Exhibit #3 is a copy of monitoring log.

TEST ARTICLE ACCOUNTABILITY:

Test article accountability was accurate. Receipt dates and quantities matched what was used. Dr Mishell received 612 tablets and used all 612 tablets, there was no product to return.

RECORD RETENTION:

Dr. Mishell maintains custody of the study records and was made aware of his responsibility with respect to record retention.

COMPUTER/ELECTRONIC DATA SYSTEMS:

Not applicable

DISCUSSION WITH MANAGEMENT:

At the conclusion of the inspection a brief discussion was held with Dr. Mishell and [redacted] but no FDA-483, Inspectional Observations, was issued. The need to maintain records which are accurate and legible was again discussed. It was explained that the records did appear

better than during the previous inspection. Dr. Mishell stated that he was aware of the importance of keeping accurate and legible records and that they would make every attempt to keep better records for future studies.

QUESTIONS IN THE ASSIGNMENT:

1. Attached as Exhibit # is a copy of the monitoring log.

2. All CRF's were compared with source documents at the site for accuracy by

3. The investigator felt that the study protocol and record keeping requirements had been adequately explained to him and was reinforced during the monthly visits to the site.

4. There did not appear to be anything left behind by the monitors after their visits to the site nor was there anything subsequently sent that was in the files. Dr. Mishell did not recall receiving any such document.

ATTACHMENTS:

1 FDA-482, Notice of Inspection, dated 12-9-99

EXHIBITS:

1 English and Spanish Informed Consents
2 Copy of IRB Approval for Advertisement and Ad Copy
3 Copy of Monitoring Log

/S/

Investigator
Los Angeles District

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

1. DISTRICT ADDRESS & PHONE NO.
19900 [illegible] 2101
Irvine, CA 92612 - 2300
949-798-7700

TO

2. NAME AND TITLE OF INDIVIDUAL: Nurse Manager

3. DATE: 12-9-99

4. FIRM NAME: Dr. Daniel Mission

5. HOUR: a.m. / 12:15 p.m.

6. NUMBER AND STREET: 1340 N. Mission Rd 2K1

7. CITY AND STATE & ZIP CODE: Los Angeles, CA 90033

8. PHONE # & AREA CODE: 323-226-3201

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

9. SIGNATURE *(Food and Drug Administration Employee(s))*
/S/

10. TYPE OR PRINT NAME AND TITLE *(FDA Employee(s))*

Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

[1]Sec. 704. (a)(1) For purposes of enforcement of this Chapter, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs or restricted devices are manufactured, processed, packed, or held, the inspection shall extend to all things therein *(including records, files, papers, processes, controls, and facilities)* bearing on whether prescription drugs or restricted devices which are adulterated or misbranded within the meaning of this Chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Chapter. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data *(other than data as to qualifications of technical and professional personnel performing functions subject to this Act)*, and research data *(other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 507(d) or (g), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(k) of the title.* A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[2]Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing – Biological Products and Clinical Laboratories and******

Sec. 351(c) "Any officer, agent, or employee of the Department of Health & Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F – ******Control of Radiation.

Sec. 360 A(a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests *(or testing programs)* required by section 355 (h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records *(including testing records)*, make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

******

(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information.