UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC)

IN JOINT SESSION WITH THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

(ACRHD)

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MEETING

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TUESDAY,

DECEMBER 16, 2003

The joint Advisory Committees met at 8:00 a.m in the Grand Ballroom of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Louis Cantilena, Jr., NDAC Chairman, presiding.

PRESENT:

LOUIS R. CANTILENA, Jr., M.D., Ph.D., NDAC Chairman

LINDA C. GIUDICE, M..D., Ph.D., ACRHD Chair

MICHAEL C. ALFANO, D.M.D., Ph.D., Acting Industry Representative

PRESENT (Continued):

NEAL L. BENOWITZ, M.D., NDAC

ABBEY B. BERENSON, M.D., Consultant (Voting)

TERRENCE F. BLASCHKE, M.D., NDAC

LESLIE CLAPP, M.D., NDAC

SUSAN A CROCKETT, M.D, ACRHD

FRANK F. DAVIDOFF, M.D., NDAC

SCOTT S. EMERSON, M.D., Ph.D., ACRHD

MICHAEL F. GREENE, M.D., Consultant (Voting)

W. DAVID HAGER, M.D., ACRHD

GERI D. HEWITT, M.D., Consultant (Voting)

JULIE A. JOHNSON, Pharm.D., NDAC

Y.W. FRANCIS LAM, Pharm.D., NDAC

VIVIAN LEWIS, M.D., ACRHD

LARRY LIPSHULTZ, M.D., ACRHD

CHARLES J. LOCKWOOD, M.D., ACRHD

GEORGE A. MACONES, M.D., ACRHD

SONIA PATTEN, Ph.D., NDAC Consumer Representative

VALERIE MONTGOMERY RICE, M.D., ACRHD

WAYNE R. SNODGRASS, M.D., Ph.D., NDAC

JOSEPH STANFORD, M.D., ACRHD

MARY E. TINETTI, M.D., NDAC

PRESENT (Continued):

JAMES TRUSSELL, Ph.D., Consultant (Voting)

LORRAINE TULMAN, RN, M.S., ACRHD Consumer Representative

DONALD L. UDEN, Pharm.D., NDAC

HENRY W. WILLIAMS, Jr., M.D., NDAC

ALASTAIR WOOD, M.D., NDAC

KAREN M. TEMPLETON-SOMERS, Ph.D., NDAC Executive Secretary

SPONSOR REPRESENTATIVES AND CONSULTANTS:

CAROLE BEN-MAIMON, M.D.

VIVIAN DICKERSON, M.D.

DAVID GRIMES, M.D.

FDA REPRESENTATIVES:
STEVEN K. GALSON, M.D., M.P.H., Acting Director, CDER
SANDRA KWEDER, M.D., Deputy Director, OND
JONCA BULL, M.D., Director, ODE V
JULIE BEITZ, M.D., Deputy Director, ODE III
DONNA GRIEBEL, M.D., Deputy Director, DRUDP
CURTIS J. ROSEBRAUGH, M.D., M.P.H., Deputy Director, DOTCDP
ANDREA LEONARD SEGAL, Team Leader,
JIN CHEN, M.D., Ph.D., Medical Officer, DOTCDP
DANIEL DAVIS, M.D., M.P.H., Medical Officer, DRUDP
KAREN LECHTER, J.D., Ph.D., Social Science Analyst, DSRCS

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

(8:05 a.m.)

CHAIRMAN CANTILENA: Good morning, everyone. We'd like to get started.

I'd like to welcome you to the December 16th, 2003, meeting of the Nonprescription Drugs Advisory Committee and jointly with the Reproductive Health Drugs Advisory Committee.

We're here today to discuss the proposition of switching Plan B from Rx to over-the-counter, and before we get started, Dr. Somers has a statement that she needs to read for all of us.

DR. TEMPLETON-SOMERS: Good morning, and welcome to this joint session of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs.

All committee members have been provided with copies of background materials from both the sponsor and the FDA and with copies of the letters from the public that were received by the December 5th deadline. The background materials were posted on the FDA Web site yesterday morning.

Copies of all of these materials are available for viewing only at the FDA desk outside this room.

Today we have a very large table, a full house, and an exciting topic. So we'd like to start with a few rules of order.

FDA relies on its advisory committees to provide the best possible scientific advice available to assist us in making complex decisions. We understand that issues raised during the meeting may well lead to conversations over breaks or during lunch.

However, one of the benefits of an Advisory Committee meeting is that the discussions take place in an open and public forum. To that end, we request sincerely that members of the committee not engage in private, off-record conversations or interviews on today's topic during the breaks or during lunch.

Whenever there is an important topic to be discussed, there are a variety of opinions. One of our goals today is for this meeting to be conducted in

a fair and open way where every participant is listened to carefully, treated with dignity, courtesy, and respect. Anybody whose behavior is disruptive to the meeting will be asked to leave.

We are confident that everyone here is sensitive to these issues and can appreciate that these comments are intended as a gentle reminder. We look forward to a productive and interesting meeting.

Thank you.

CHAIRMAN CANTILENA: Okay, and as I said earlier, my name is Dr. Lou Cantilena, head of clinical pharmacology at the Uniformed Services University. I'll be chairing this meeting.

And we'd like to go around so that everyone can introduce themselves, and we'll start on this side.

DR. ALFANO: Michael Alfano, Dean of the Dental School at New York University.

DR. HAGER: David Hager, Reproductive Health Drugs, from the University of Kentucky.

DR. LAM: Francis Lam from University of Texas Health Science Center in San Antonio, a member

of NDAC.

DR. LIPSHULTZ: Larry Lipshultz, Professor of Urology, Baylor College of Medicine.

DR. JOHNSON: Julie Johnson from University of Florida Colleges of Pharmacy and Medicine, from the Nonprescription Drug Committee.

DR. MACONES: George Macones. I'm Associate Professor of OB-GYN and Epidemiology at the University of Pennsylvania on Reproductive Drugs.

DR. PATTEN: Sonia Patten. I'm a consumer representative. I'm an anthropologist on faculty at Macalester College in St. Paul, Minnesota, and I'm part of the Nonprescription Drug Committee.

DR. CROCKETT; I'm Susan Crockett. I'm a general OB-GYN Director of Maternity Services for the CHRISTUS Santa Rosa Family Practice Residency Program, and I'm a member of the Reproductive Health Drugs Committee.

DR. UDEN: I'm Don Uden, a professor at the University of Minnesota College of Pharmacy and member of NDAC.

DR. STANFORD: Joseph Stanford, University

of Utah, Department of Family and Preventive Medicine on the Reproductive Health Drugs Committee.

DR. BENOWITZ: Neal Benowitz. I'm an internist and clinical pharmacologist from U.C., San Francisco, on the Nonprescription Drug Committee.

DR. LOCKWOOD: Charles Lockwood, Chair of OB-GYN at Yale and Reproductive Drugs.

MS. TULMAN: Lorraine Tulman, Associate Professor, University of Pennsylvania School of Nursing, Reproductive Health Advisory Group, and I'm the consumer representative for that group.

DR. TRUSSELL: James Trussell from the Office of Population Research at Princeton University.

DR. GIUDICE: Linda Giudice, reproductive endocrinologist and Professor of OB-GYN at Stanford University, and Chair of the Reproductive Health Drugs Committee.

DR. TINETTI: Mary Tinetti, Department of Medicine, Yale, Nonprescription Drug Committee.

DR. HEWITT: I'm Geri Hewitt, Assistant Professor of the Department of OB-GYN and Department of Pediatrics at Ohio State College of Medicine.

DR. GREENE: I'm Michael Greene, Professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School.

DR. CLAPP: Leslie Clapp, pediatrician, Buffalo, New York, and Clinical Associate Professor of Pediatrics, University of Buffalo.

DR. SNODGRASS: Wayne Snodgrass, Department of Pediatrics, University of Texas in Galveston, and clinical pharmacology on the Nonprescription Drug Committee.

DR. LEWIS: Vivian Lewis, Professor of OB-GYN at University of Rochester, and I'm on the Reproductive Health Drugs Committee.

DR. BLASCHKE: Terry Blaschke, internist/clinical pharmacologist, Stanford.

DR. WOOD: I'm Alastair Wood from Department of Medicine, Department of Pharmacology at Vanderbilt, and I'm on NDAC.

DR. EMERSON: Scott Emerson, Professor of Biostatistics at the University of Washington on Reproductive Drugs.

DR. BERENSON: Abbey Berenson, Professor

of OB-GYN and Pediatrics at University of Texas Medical Branch at Galveston.

DR. DAVIDOFF: I am Frank Davidoff. I'm the editor emeritus of the Annals of Internal Medicine; also now the executive editor at the Institute for Health Care Improvement, and I'm on the NDAC.

DR. MONTGOMERY: Valerie Montgomery Rice, Professor and Chair of Obstetrics and Gynecology, Meharry Medical College, and I'm on the Reproductive Health Drugs.

DR. GRIEBEL: Donna Griebel, Deputy, Division of Repro. and Urologic Drug Products, FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy of Over-the-Counter Drug Products.

DR. BEITZ: Julie Beitz, Deputy Director, Office of Drug Evaluation III, CDER, FDA.

DR. BULL: Good morning. Jonca Bull, the Director of the Office of Drug Evaluation IV in CDER, FDA.

DR. GALSON: Steve Galson. I'm the Acting Director of the Center for Drug Evaluation and

Research.

DR. KWEDER: I'm Sandra Kweder. I'm the Deputy Director of the Office of New Drugs in CDER.

DR. TEMPLETON-SOMERS: Thank you. I'm Karen Templeton-Somers, Executive Secretary to the Committee, FDA.

And the following announcement addresses conflict of interest issues with respect to this meeting and is made a part of the record to preclude even the appearance of impropriety at the meeting.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their own or their employer's financial interests. All participants have been screened for interests related to the product, competing products and companies that could be affected by today's discussions The agency has reviewed the interests reported by the committee participants and has determined that there is no potential for a conflict of interest at this meeting.

We would like to disclose that Dr. Michael Alfano is participating as the acting industry

representative, acting on behalf of Regulated Industry.

In the event the discussions involve any other products or firms not already on the agenda for which 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 address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Somers.

We'll now hear from Dr. Sandy Kweder, who will open the meeting for the FDA.

DR. KWEDER: Well, good morning, everyone, and welcome. I'd first like to start off the meeting by acknowledging the large size of the panel today and thanking all of you on the panel for coming here. Sometimes a large panel makes interchange more

difficult, but I think Dr. Cantilena is probably up to the challenge.

Your discussion is extremely important to us, but before you begin that, I'd like to provide some background perspective as to how we got here.

Following my remarks, Dr. Curt Rosebraugh will introduce the subject in more detail and get on with some of the scientific presentations.

First, let me be clear that we're here today to discuss the scientific data available to address Barr Lab's application to remove the prescription requirement for their product Plan B. Plan B is an emergency contraceptive that is indicated for use in the unexpected circumstance when another standard contraceptive method fails or fails to be used.

While previously established safety and efficacy data for this medication will be referenced, you'll be asked to consider these data only as they relate to Plan B's suitability for nonprescription status. You'll hear a lot more about FDA's general approach to making decisions about switches from

prescription to nonprescription status. So I'm not going to address that further.

But, secondly, I would like to assure you that we at FDA recognize the broad array of issues related to emergency contraception, in general, that may arise in your discussion. None of these are new.

In June of 2000, FDA, CDER particularly, held a Part 15 hearing. The purpose of that two-day hearing was solely to solicit public testimony on the future of prescription to nonprescription product shifts. We requested that experts and any concerned member of the public come and share their perspectives in several areas.

What products should and should not be considered for nonprescription status?

What are the perceived incentives and perceived barriers to such shifts?

And outstanding issues, what are they that might be addressed to modify incentives and barriers?

I was part of the FDA panel listening to that testimony. In addition to other product groups discussed, like cholesterol lowering agents, non-

sedating antihistamines and antihypertensives, we heard several hours of testimony regarding oral contraceptives as potential candidates for being available without a prescription, but in particular, many speakers favored or did not favor making emergency contraception nonprescription.

Those in the favoring group pointed out that the clinical safety of the product and the importance of access to emergency contraception are the keys to maximizing its effectiveness. For example, if the product is to be used as directed, the woman must be able to take it within 72 hours of intercourse. This is often not achievable given our current system of pharmacy practice.

They also cited studies in the literature which showed that women do not appear to substitute emergency contraception for other more traditional forms of contraception.

Those who did not favor nonprescription status raised public health concerns about potential effects of wider availability of the product on adolescent health and behavior. For example, these

speakers did not find the published literature convincing with regard to the impact of more readily available emergency contraceptives on adolescent behavior. Of particular concern to them were whether nonprescription access would increase sexually transmitted infections and decrease the use of other more effective contraceptives or even affect choices about sexual behavior in adolescent groups.

We at FDA understand the complexity and the multiple perspectives on these matters. We will consider their full breadth before arriving at any final regulatory decision following this meeting.

Finally, I want to say a few words about seeking answers to difficult questions and decision making. One of the things that we at FDA do when we're faced with one is we often look to others' experiences to see what has happened with those who have gone before us.

For example, we look to the experience of products as they may be marketed in other countries. Some of those experiences may come up today in the presentations and your discussions. You may be

reassured by these or frustrated because there are not detailed data to answer questions you might like to have addressed.

Please keep in mind that considering the effects of nonprescription or prescription medicines in countries other than the United States is fraught with challenges of interpretation because of differences in pharmacy models.

For example in some countries having things, what might be called behind the country, only means that a person has to ask for them. For example, in those countries this status is applied to hundreds of medicines. The open shelves in the shop are there only for toiletries and other supplies.

In these countries, including many in Europe, most of the products that we routinely consider over-the-counter and readily available even in a grocery store are distributed in this manner at a pharmacist's counter, as are many products that we are used to only having available by prescription.

In other countries, the term "behind the counter" refers to the need to request the product of

a pharmacist and obtain or have the opportunity to be counseled by a pharmacist.

The bottom line is that data from these countries can only be looked at from an arm's length, and they do not necessarily translate into data that give solid answers to bigger picture questions that we or you may have. We just have to do the best we can.

Again, thank you for coming and for your willingness to help us with a challenging decision. Discussions at these meetings are as important, if not more important, than any vote tally on the formal questions that we pose, and we're looking forward to your discussion today.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Kweder.

Dr. Rosebraugh, would you like to continue with the FDA introduction, please?

DR. ROSEBRAUGH: Good morning. On behalf of the Divisions of Over-the-Counter Drug Products and Reproductive and Urologic Drug Products, I'd like to welcome the members of each respective Advisory

Committee to today's meeting regarding the nonprescription status of Plan B.

By way of introduction, I would like to briefly go over the regulatory history of Plan B, go over the regulatory requirements for nonprescription marketing of drug products, and outline today's agenda.

Plan B was approved for prescription use on July 28th, 1999, for the indication as an emergency contraception to be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Prescription directions for use indicate that to obtain optimal efficacy, the first does needs to be taken as soon as possible within 72 hours of intercourse, and the second dose needs to be taken 12 hours later.

Women's Capitol Corporation, the applicant for the original prescription NDA, submitted an application for Plan B switch from prescription to nonprescription status in April of 2003. As the efficacy of Plan B, when used as per directed has already been established and the sponsor is not

seeking a new indication or dosage regimen, this will not be a topic at today's meeting.

However, the efficacy based on a use in a nonprescription setting is of interest to us.

The purpose of today's Advisory Committee meeting is to determine whether Plan B meets regulatory requirements for nonprescription marketing.

Regarding nonprescription requirements or requirements for nonprescription marketing, the Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act, which was enacted in 1951, formally differentiates between prescription and nonprescription drugs. This is articulated in the Code of Federal Regulations 21 CFR 310-200(b) and states, "Any drug limited to prescription use under Section 503(b)(1)(C) of the Act shall be exempt from prescription dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of public health by reason of the drug's toxicity or other potentialities for harmful effects, the method of its use, or the collateral measures necessary to its use, and he finds that the

drug is safe and effective for use in self-medication as directed in the proposed labeling."

So the bottom line is this regulation provides that a drug be sold nonprescription if it is safe and if adequate directions for use can be written that are discernable to a lay person.

When approaching a possible prescription to nonprescription switch candidate, there are several questions that the agency takes into consideration to assess whether the product is, indeed, a suitable switch candidate. Regarding the questions that we take into consideration, we wonder if the product has an acceptable safety margin, as demonstrated from prior prescription marketing experience; whether it has low misuse and abuse potential, a reasonable therapeutic index of safety; whether the condition that it is being used for can be adequately self-recognized and self-treated with minimal health care provider intervention; whether the benefits outweigh the risks; and when the product used under nonprescription conditions, is it safe and effective?

If the answer to the above questions are

yes, then the proposed product may meet regulatory requirements for nonprescription safety and effectiveness and is a candidate for consideration of nonprescription marketing.

In order to address the questions that face switch candidates, the Plan B switch NDA application components included summaries from previously existing data and newly conducted studies. To address the safety profile and misuse and abuse potential of the product, the sponsor has submitted safety data from their original NDA and a review of post marketing safety, both foreign and domestic, and a review of the published literature.

To evaluate consumers' ability to self-recognize the condition they are treating and whether self-treatment with the product is safe, the sponsor has conducted label comprehension and actual use studies. We will be hearing greater detail about these things during this morning's presentations.

This type of data and the studies that the sponsor has performed are consistent with other submissions that have been evaluated in the past where

the switch did not involve a change in dosage or indication.

To review today's agenda, we will begin with a presentation by the sponsor, and that will be followed by a question and answer session.

Then following a break, we will have presentations by the FDA. Dr. Dan Davis will be presenting the FDA's review of safety. Dr. Karen Lechter will be presenting the FDA's review of the label comprehension study, and Dr. Jin Chen will be presenting the FDA's review of actual use studies and the literature review.

That will then be followed by a question and answer session of the FDA.

We will then have an open public hearing, then a much deserved lunch, and finally we will dedicate the afternoon to the panel discussion.

During the presentations the joint committee members should consider the information and use the question and answer session to prepare to answer the questions posed to the committee regarding the possible prescription-to-nonprescription switch of

Plan B.

With that as a background, the agency looks forward to today's discussion.

CHAIRMAN CANTILENA: Thank you, Dr. Rosebraugh.

Okay. At this time we will move to the sponsor presentation, which will be led by Dr. Ben-Maimon from Barr.

Dr. Maimon, if you would start and then as you go through you can introduce the other members of your team.

For the committee, we'll hold our questions until the end of sponsor presentation.

Thank you.

DR. BEN-MAIMON: Good morning, everybody. I'd like to start by just thanking the panel, the FDA, for giving us this opportunity to present the data supporting the prescription to over-counter switch. We're all very interested, as the FDA stated, in hearing the panel's discussion and comments, and of course, interested in answering as many of the questions as we possibly can.

I'm Carole Ben-Maimon, President/COO of Barr research.

You may have heard that Barr Laboratories has signed a letter of intent to acquire the assets of Women's Capitol Corporation. That includes Plan B for emergency contraception. That transaction has not yet closed, and so today I'm actually representing Women's Capitol Corporation.

A little bit about what I'm going to cover in the presentation today. First, the background, a little bit of an overview, and a discussion about how Plan B prevents pregnancy. I'll talk a little bit about the rationale for the over-the-counter switch, try and not duplicate what was already said, and then I'm going to turn the podium over to Dr. Vivian Dickerson, who is the President-elect for the American College of Obstetricians and Gynecologists, for her to discuss with you the benefit-risk assessment as ACOG sees it.

I'll return to the podium and give you some background on our clinical trials, the label comprehension and actual use, and then Dr. David

Grimes, Vice President of Biomedical Affairs at Family Health International and clinical professor at the Department of Obstetrics and Gynecology at the University of North Carolina School of Medicine, will give a presentation and discuss the health consequences of an OTC switch for Plan B.

Finally, I'll return to the podium and discuss with you our CARE Program, which many of you saw in the briefing document. That program is really designed to increase access and awareness, as well as availability of Plan B, and I'll discuss some of the rationale and the presentation for that.

What is emergency contraception? Emergency contraception is therapy for women who desire prevention of pregnancy, have had unprotected sexual intercourse, including contraceptive failures and sexual assault.

It's really important that we look at this in the context of what's going on in this country today. Fifty-three percent of unintended pregnancies occur in women who are using contraceptives. These are method failures or user failures, condoms that

break, slip, women who miss their pills, but clearly, 53 percent of the unintended pregnancies are in women who have been using contraceptives.

Unplanned pregnancies are a major health care problem in this country. There are over three million unintended pregnancies in the United States each year. With typical use, 15 percent of women who are using condoms will be become pregnant each year and eight percent of those using oral contraceptives will become pregnant each year.

Half of the unintended pregnancies in this country will result in abortion. It is estimated that up to 50 percent of these pregnancies could be prevented with greater access and use of emergency contraception.

There are two approved products today in the United States: Preven, which was approved in 1998, and Plan B, which you already heard was approved in 1999.

I hope they're not putting you to sleep.

Preven is a combination product with an ethinyl estradiol, and Plan B is actually just a

levonorgestrel product, a progestin only product, and that's really of significance as we get into how these products prevent pregnancy.

But you can see that the regimens are essentially identical. Both have to be taken within 72 hours of the active unprotected sexual intercourse, and the second tablet has to be taken 12 hours later.

The most fertile days of the female cycle, the menstrual cycle, are the five days leading up to ovulation and then 24 hours after, and within 24 hours of ovulation, the egg is no longer viable and fertilization cannot occur.

Plan B works like other progestin only oral contraceptives and prevents ovulation. Plan B is an oral contraceptive, not an abortion pill. The direct evidence is highly in favor of the fact that the primary mechanism of action, if not the sole mechanism of action, is prevention of ovulation.

There are two hypothetical mechanisms that have been proposed: interference with fertilization and interference with implantation, but for levonorgestrel only contraceptives, levonorgestrel

only emergency contraceptives, there is no data to suggest that either of these are impacted, either of these events are affected by Plan B.

Again, I would reiterate Plan B works by preventing ovulation. It is an oral contraceptive, not an abortion pill.

What's really critical when we consider the over-the-counter switch of Plan B is this chart, and what this is is the data from the efficacy trial that was included in the original NDA that supported the approval of the prescription drug product, and this was the WHO study that was done in the late '90s.

And what it shows is that if Plan B, if the first tablet is taken within 24 hours of the active unprotected sex, the pregnancy rate is as low as .4 percent. Many of you may know that with a single act of mid-cycle sex the pregnancy rate is about eight percent. So clearly, the reduction is significant within the first 24 hours.

If a woman waits until 48 to 72 hours, the pregnancy rate rises to 2.7 percent. It is imperative that women have access to this product quickly so that

they can maximize its effect.

What does the prescription requirement do? Well, it creates delays. The woman needs to identify the need, clearly a need that is easily identified by most women given the fact that they have either had a contraceptive failure, coercive sex or rape, or unprotected sex.

They need to then locate a prescriber who is willing to prescribe emergency contraception for them. Again, we can't forget that most of these events are not occurring between nine to five Monday to Friday. They're occurring at night and on weekends, and so this is not always an easy undertaking.

They have to call the prescriber. They have to talk to the prescriber. The prescriber then has to call them back and decide to prescribe the product.

If a woman does not have a physician that she sees regularly or somebody that follows her regularly, the doctor may want for them to come into the office and be examined because clearly, doctors

are reticent sometimes to calling in prescriptions to patients who they don't know and probably for good reason.

And so once she gets her prescription, she now has to go to pharmacy, and at the pharmacy I can tell you and will show you data to support this, not a lot of pharmacies stock this product, and the reason is the volume and the demand are quite low to date because awareness is low. So just finding a pharmacy where she can obtain the product in a timely fashion can also be a challenge.

And finally, she can purchase the product. So the prescription setting actually creates significant barriers and time delays as we go through the process.

With that, I'm going to turn the podium over to Dr. Dickerson. Dr. Dickerson is President-elect of the American College of Obstetricians and Gynecologists. She is the Director of Obstetrics and Gynecology at the University of California Irvine Medical Center, and with that, Dr. Dickerson.

DR. DICKERSON: Good morning. My name is

Vivian Dickerson, and I am an Associate Professor at the University of California-Irvine and Director of the General OB-GYN Division at UCI Medical Center.

I have no financial interests or potential conflicts of interest to disclose in this case.

As President-elect of the American College of Obstetricians and Gynecologists, I am representing ACOG in support of over-the-counter status for Plan B. The college rarely presents product specific testimony. However, we are delighted to have the opportunity to present today because we strongly believe that Plan B meets the FDA criteria for over-the-counter status, and because there is a public health imperative to increase access to emergency contraception.

ACOG's mission is to improve health care of women. We pursue that mission through education and advocacy. On behalf of ACOG, a national organization representing over 45,000 members who provide health care for women, I am speaking today to encourage the FDA to act favorably and quickly on the Women's Capitol Corporation/Barr Laboratories

application to make Plan B available to women over the counter.

Plan B is safe, and it is effective. It is not teratogenic. It has no potential for overdose or addiction. It does not require special medical screening. It is easy to use, and the labeling instructions are clear and understandable.

We know that Plan B works. It prevents pregnancy. By preventing unintended pregnancy, it also prevents abortion.

We know that women use it correctly and are very unlikely to substitute it for an ongoing method of birth control. For these reasons, ACOG supports the removal of the prescription requirement for Plan B for all women of reproductive age.

As an OB-GYN who has seen thousands of patients over the past 20 years and as a spokesperson for an organization to which 95 percent of all Board certified OB-GYN's in the United States belong, I would like to take the opportunity to clarify why a clinician does not need to oversee a woman's use of Plan B and why women of reproductive age should have

access to it.

I think it's important that everyone understand why timely access to Plan B is imperative. Now, this may be a review for most of us, but let me begin by talking about how pregnancy occurs.

First, there must be normal maturation of sperm and egg. Following release into the vagina, the sperm are transported through the cervix, uterus, and fallopian tube. Capacitation of the sperm occurs in the tube in preparation for fertilization of the egg. After ovulation the egg is transported from the ovary to the fallopian tube.

Fusion of the sperm and egg occurs in that tube, and the fertilized egg is transported to the uterus. During transport, the fertilized egg begins to divide until it reaches the blastocyst stage, at which time it implants into the lining of the uterus. This is the point at which pregnancy begins.

It can take five to nine days from the time of fertilization for implantation to actually occur.

Clinical research data demonstrate that

Plan B primarily prevents pregnancy by inhibiting or preventing ovulation and secondarily perhaps by impairing the migration and function of sperm. In other words, it prevents pregnancy prior to fertilization.

Plan B is, therefore, most effective when used within 24 hours of unprotected intercourse, although it has been shown to prevent pregnancy for up to three days, and recent data show that it may even work for up to five days after unprotected intercourse.

Each Plan B tablet contains three-quarters of a milligram of levonorgestrel, which is a synthetic progestin contained in many current oral contraceptives. The safety and efficacy of levonorgestrel as a daily contraceptive or a postcoital backup are well established. Indeed, the only absolute contraindication to Plan B is a known or suspected hypersensitivity to the product.

If a woman takes Plan B while pregnant, it will not cause an abortion, nor is there evidence that it increases teratogenicity.

Unintended pregnancy is a substantial problem in the United States. Nearly 50 percent of the 6.3 million annual pregnancies in the U.S. are unintended due to either method failure or failure to use a method.

It is important to recognize that unintended pregnancy does not discriminate. It affects women of all ages, from teenagers to women in their 40s. It is equally as important to recognize that not all women, and adolescents, in particular, have control over the occurrence of intercourse or the use of contraception. Examples of such cases are rape, date rape, partner pressure, or other socio-cultural pressures to engage in sex without contraception.

Overall it is estimated that widespread use of emergency contraceptive pills has the potential to decrease by at least 50 percent the current incidence of unintended pregnancies and subsequent abortions.

Nonetheless, Plan B is no substitute for ongoing methods of contraception, such as the IUD, the

birth control pill, or injectable contraceptives, all of which have a higher proven efficacy.

One of the major barriers to the use of emergency contraception is timely access. By removing the prescription requirement, women will be more likely to obtain emergency contraception when it is most effective. Data show that women who had emergency contraception on hand were more likely to use it than women who were simply told about the product or even given a prescription.

However, these data indicate that women do not substitute emergency contraception for an ongoing form of birth control, and this applied to teens as well.

Requiring a prescription for emergency contraception is, in fact, an unnecessary barrier to obtaining and using the product in a timely fashion. Women know when they may be at risk for pregnancy, and the actual use and label comprehension studies indicate that women understand how to use emergency contraception, and that they use it correctly.

A switch to over-the-counter availability

of emergency contraception will have a tremendous impact on access to this vital and easy to use therapy.

The label comprehension data also demonstrate that women clearly understand that emergency contraception does not protect against sexually transmitted infections or HIV. There are no data suggesting that women who use emergency contraception are less likely to obtain necessary health services.

In conclusion, on behalf of our 45,000 members who care for women every day, ACOG strongly supports making Plan B available over the counter to all women of reproductive age. If we are truly dedicated to lowering the number of unintended pregnancies and abortions in this country, let's prove it by making Plan B an emergency contraceptive available over the country.

Thank you very much.

DR. BEN-MAIMON: Thank you, Dr. Dickerson.

I'm going to go through very quickly what you've already heard. There are the requirements for

the approval of a product to make a prescription to over-the-counter switch.

The produce has to have an acceptable safety profile based on the prescription use and the prescription experience. It has to have a low potential for abuse and misuse. It has to have an appropriate safety index, therapeutic index, as well as a positive benefit-risk assessment.

And finally, it has to be for a condition that is self-recognizable, self-limiting, and requires minimal health care practitioner intervention.

With that, Plan B clearly meets the requirements for OTC use. The post marketing and clinical safety trial data demonstrate an acceptable safety profile in a large number of women who have been exposed to the product. There is a low potential for abuse or misuse. There is no question that the benefits of over-the-counter availability strongly outweigh the risks, and finally, based on the label comprehension studies and the actual use studies, the product has been demonstrated to be or women have demonstrated that they can properly self-select,

determine when they need it, how to use it, and they can use it correctly.

There is really no medical reason why Plan B should not be sold over the counter. Over 7,000 women have been exposed to Plan B in clinical trials, and you can see that the vast majority of these trials have used the .75 times two. There were two additional doses in some of the trials, but the vast majority of those 7,000 women have been exposed to the identical regimen that we're talking about here today.

Plan B in these trials has been shown to be 89 percent effective in preventing pregnancy if taken within the first 72 hours of unprotected sex. It reduces the pregnancy rate from eight percent to just over one percent.

The safety profile is also demonstrated. It is well described. The most common side effects are nausea, abdominal pain, fatigue, and all of these are self-limited. Most of them are mild to moderate, and very few, if any, require intervention from a health care practitioner.

There have been no deaths associated with

Plan B.

And finally, there is no increase in the incidence of ectopic pregnancy. Professional screening cannot impact the adverse events or the efficacy of the product. As you heard from Dr. Dickerson, the intervention of a health care practitioner before or immediately after does not in any way change the outcome. Most of the events, as I said before, the adverse events are self-limited. They resolve on their own, and the efficacy cannot be impacted by anything except taking it more quickly.

And the critical issue here is that to maximize the effect, women need to have access to it.

With regard to ectopic pregnancy, there has been some discussion as to whether or not there's an increased rate of ectopic pregnancy with Plan B, and this comes from the fact that Plan B is a progestin only emergency contraceptive, and oral contraceptives that when taken continuously, progestin only oral contraceptives, have been questionably associated with an increased incidence of ectopic pregnancy.

There are six trials in over 7,000 women where they systematically followed women and followed the pregnancies and their outcomes. There were 133 pregnancies with only two ectopics. That gives us a rate of about one and a half percent. The background rate in the general population is about two percent. So in a large number of women there is clearly no increased incidence of ectopic pregnancy that has been demonstrated.

In post marketing studies, as well, there are over six million women worldwide who have been exposed to Plan B, and if you look at the exposures and calculate the number of pregnancies anticipated, there is no increased incidence of ectopic pregnancy.

Again, there is no medical reason why Plan B should not be sold over the counter.

Our two trials that you've heard us allude to are a label comprehension study and an actual use study, and I'm going to go through that data now and show you that women can self-select and take the product correctly.

The first study is a label comprehension

study that was done in order to determine whether women could read and understand the label in an over-the-counter setting. Women 12 to 50 years of age were included in those trials, and it was performed primarily at malls. There was a sampling of minority women, as well as young women and women with lower educational levels, as well as lower literacy levels, and it was a questionnaire type study.

You can see from this slide the demographics. Here you see the age distribution. We had a large sample of young women 12 to 16. Over half of the population was 17 to 25, the most likely age group to use Plan B. There was a large sample of diverse ethnic groups represented in the United States, and we applied the rapid estimate of adult literacy in medicine test to women. Women took that test who were over 18 but had not completed college. So there was a subset of 395 women who were evaluated for literacy. About 35 percent of those scored in the less than eighth grade literacy category, and this is a way of looking at whether or not women with low literacy can understand the product label.

There were 11 objectives in this trial. There were communication objectives that we were trying to determine whether women understood, and I'm not going to go through them. You actually have in front of you a handout that has all of the 11 objectives, and I'll be referencing that handout as I go through the presentation.

But you can see that the first couple dealt with what the product is intended to do and to be used for. There was a question about sexually transmitted infections and AIDS, how the product is used, and then the side effect profile.

Here this chart shows you the 11 objectives along the bottom. This is the percent of women that were able to answer correctly, and clearly the vast majority, the overwhelming majority of women were able to answer all of the objectives correctly.

The one that had a slightly lower rate of understanding percent of women was objective number two, and I'll talk about that objective in a couple of minutes.

This chart looks at the same 11 objectives

along the bottom, and the yellow represents the 12 to 16 year olds, the pink the 17 to 25 year olds, and the blue the 25 to 50 year olds, and then the dot is the actual average, which you saw in the previous slide.

If you look across the overwhelming majority of women were able to understand all of these objectives, and really the only one that showed a trend with a lower understanding, a lower comprehension level in the younger group was objective number two.

This looks at the distribution by literacy level, and the yellow represents the lower literacy women, with the pink representing the women with literacy levels greater than eighth grade, and you can see, again, objective number two has a difference between the two groups, and you might suggest that objective number four also, and I'll be talking about those.

I'm sorry. I also forgot to mention objective number eight, which was also slightly lower on the overall than the others and also shows a distribution.

This, if you refer to your sheet, this objective was the objective that discussed unexplained vaginal bleeding, and at this point in the prescription label unexplained vaginal bleeding is a contraindication. Through discussions with the FDA with regard to this contraindication, it has been decided that this will no longer be a contraindication. It will be a warning. Women should follow up with their health care practitioners if they continue to have unexplained vaginal bleeding, but it will not be and it is not a contraindication to the use of Plan B. So this really goes away, which is why I've sort of ignored it.

Objectives, and I know this is a busy slide. So let me just walk you through it a little bit. Plan B is intended as a backup method and not for regular contraception. That was the objective that was meant here.

Women had to get at least three of these questions correct in order to be counted as having understood the objective. You can see the distribution by age here, and then question number

nine, 21, 22, and 25 were the questions that were relevant.

Question number nine and number 22 are direct questions. According to the label, should Plan B be used as a regular form of birth control? And you can see that most women were able to answer both these questions correctly.

The two situational questions here, where we were talking about situations where the partner doesn't want to use condoms and is it for routine birth control or not; these questions women scored lower.

And we have a couple of hypotheses why that may have been. Clearly, the situational questions were more difficult for women to answer. Was it a result of the fact that we used the terminology "husband," where husband implies a monogamous, long-term relationship and pregnancy may not be such a big deterrent?

There could be any number of reasons why women didn't answer these two questions correctly, but clearly, those were the two questions that made it

difficult, whereas the direct question suggests that they do understand that it is not a routine form of birth control.

With regard to the lower literacy group, you see the same trend. Question nine and question 22 they do quite well on, but, again, in the lower literacy group there is a trend towards less understanding of the two situational questions.

What we tried to do to deal with that was bold the label, and I know it's hard to see here because of the quality of the PDF, but it's on the board, and I'll be handing out a package to you in a little bit and you'll be able to look at it in your hands.

But we have bolded Plan B should not be used in place of regular contraception. In addition, this is a message that we will be trying to drive home with our ancillary materials through our CARE Program to insure that women do understand that they need to use routine forms of birth control.

This was objective number four, and if you remember, there was some difference between the lower

literacy group and the higher literacy group. This question they had to get this number ten correct in order to be able to be counted as correct, and you can see that all of the other answers were correct.

The objective here is that the first pill should be taken within 72 hours, and you can see that the correct answer to ten was as soon as possible and within three days, if they answer that, or within three days. But as soon as possible was not counted as a correct answer because we wanted to see the 72-hour time point.

And clearly that weighs in, and some women -- this was an open-ended question. They had to fill it in. It was not multiple choice -- and so some women put as soon as possible and didn't put within 72 hours, and that clearly is what happened here, and the results of the as soon as possible are down below. So really women do understand that they need to take it within 72 hours, and that is clearly demonstrated in the actual use study, and I'll show that to you in a minute.

So with regard to the results of this

study, the intent to treat analysis shows that we had satisfactory responses to all objectives, 80 percent or greater correct responses to nine of the 11 objectives, and the two objectives that were not answered correctly, one of them was the unexplained vaginal bleeding, which is no longer a contraindication and, therefore, no longer relevant.

Finally, in conclusion, the study demonstrates adequate label comprehension, and based on the results and in an effort to insure we had the best label we possibly could, we did make some minor changes before the actual use study and, therefore, enhanced we hoped the understanding and the ability to use the product correctly.

And these just included bolding emergency contraception to make sure that women understood it was for an emergency; bolding a serious medical problem. This section relates to severe abdominal pain, and we wanted to make sure that women understood that if they were experiencing severe abdominal pain, they needed to follow up with a physician because it might be the sign of an ectopic pregnancy.

We bolded the 12 hours to make sure they understood they had to take the second tablet within 12 hours, and we changed the term "birth contraception" to "birth control."

That was the label then that was employed in the actual use study and was used in the actual use study. The actual use study was intended to demonstrate whether or not, to find out whether women could self-select. Could they determine that they had a need and then identify that they needed the product, go get it, and then use it correctly?

We did this study at five Planned Parenthood affiliates and five pharmacies. The pharmacies were all in Washington State. That's because Washington State has a pharmacy access program. So it was feasible to do it there. Other states were not feasible.

The way it worked was women came in, and they said, "I need emergency contraception," and they were then told that there was a study going on and did they want to participate. If they said they did, they were handed the package closed and sealed with the

drug facts panel on the back. They were then asked to review that and decide whether or not Plan B was right for them.

If they decided that it was, they then signed an informed consent, and they received the product and a data card and were followed up in one and four weeks.

You can see here the demographics. This is the actual use study. This is the label comprehension study. This is all U.S. women 14 to 44, and what you see here is that we have a large sampling of women 17 to 25, which is the population we would expect being most likely to use Plan B, and clearly a nice number of young women, and then a distribution throughout. And obviously all of the ethnic groups in the United States are presented, well, not all, but most.

The way it worked, there were 665 patients screened; 585 were enrolled and 80 were not. They decided not to participate. Forty-two were completely lost to follow-up. We have no data. Five hundred and forty-three provided data. Three of these women did

not take the Plan B. So their information is not included because obviously if they didn't take it, we don't have times of pill taking and stuff.

There were 540, therefore, that supplied us data. Of those, 506 supplied us all three times, the time of sex, the time of the first pill, and the time of the second pill. Five hundred and twenty-three gave us the first and the second pill, and 509 gave us the time between the sex act and the first pill.

So we looked at contraindications. The three contraindications for use are: are you already pregnant? Again, as Dr. Dickerson said, there's no data to suggest that Plan B has any teratogenicity or will have any kind of a negative impact on the pregnancy, but clearly once you're pregnant, you're pregnant. We can't prevent the pregnancy, and so there's no reason to take it.

The contraindication clearly of allergy to any of the ingredients, and finally the unusual vaginal bleeding which will no longer be a contraindication.

Ninety-nine percent of the women who took the product took it without any contraindications. There were only seven women out of the 540 who had a contraindication. One woman was pregnant, and there were six who had unexplained vaginal bleeding, again, no longer a contraindication.

So the vast, vast majority, almost all of the women were able to take it without a contraindication and understood the contraindications.

Could they take it correctly? If you look here, the first pill less than 72 hours after the sex act, 98 percent of the women took the first pill within the 72 hours after the act of unprotected sex. The second pill, the criteria for correct was exactly 12 hours. There was really no latitude, and so 74 percent of the women were able to take the second pill at exactly 12 hours.

To take both pills correctly were 72 percent. So almost all of the women were able to take the product correctly, and one of the things I think is important to note is that this is the same dose and the same regimen as the prescription drug product.

And so you can presume that if the distribution in timing that the women take the doses of these pills is similar or the same as the WHO study which supported the safety and efficacy of the product, you can anticipate that the efficacy and the safety will be the same or be similar.

And so we looked at the data in the actual use study for each pill and compared it to the WHO study, the distribution, and you can see less than 24 hours, 25 to 48 hours, 49 to 72 hours, and greater than 72 hours. The distribution, percent of women taking it in each of those time frames -- and this is the first pill -- is very, very similar to the WHO study.

The same holds for the time between the first and second pill, less than 12 hours, 12 hours, 12 to 16, and greater than 16. Again, the distribution is very similar between the two trials.

So we can anticipate that the efficacy and the safety profile should be the same as that that was described and ultimately approved in the pivotal trials that supported the NDA.

With regard to pregnancy, there were ten pregnancies in the trial. That gave us a pregnancy rate of about 1.9 percent. If you remember, the WHO study had a pregnancy rate of just over one percent, very similar. Of the ten pregnancies, four ended in abortion and six were lost to follow-up.

So, in conclusion, the study design simulates the OTC environment. Women were able to come in on their own and identify the need. Subjects were representative of the OTC setting. We had a distribution both in age and various ethnic groups. Subjects were able to self-select. They knew they needed the product. They came and they got it. They took it home, and they were able to use it correctly.

The results are similar to the WHO pivotal study, and thus, Plan B should be as safe and as effective in the OTC setting as it is in the prescription setting.

With that I'm going to turn the podium over to Dr. Grimes to discuss with you the health consequences of over-the-counter levonorgestrel. Dr. Grimes is Vice President of Biomedical Affairs at

Family Health International. He is clinical professor at the Department of Obstetrics and Gynecology at the University of North Carolina School of Medicine, and he is one of the few OB-GYNs in the country who are double Boarded in preventive medicine and in OB-GYN.

So with that I'll turn the podium over to him.

DR. GRIMES: Thank you, and good morning.

I begin with a most important message first, and that is that easy access to emergency contraception improves the health and lives of women. It does this through preventing unintended pregnancy with its serious consequences.

For many women the news of a pregnancy is a wonderful gift. Such women readily and happily accept the discomforts, inconvenience, expense, and risks involved with childbearing. Not so for women with an unplanned and unwanted pregnancy. What are the medical consequences for them?

The traditional way in which we assess the safety of childbearing around the world is the maternal mortality rate. Despite impressive progress

in recent decades, childbearing remains risky business in the United States of America.

These are the most recent data from the Centers for Disease Control and Prevention in Atlanta. As of 1999, the reported maternal mortality rate was 13 maternal deaths per 100,000 live births. If one corrects this for under reporting of such deaths, the true figure is closer to 20 deaths per 100,000 live births.

What this means is that during the past decade over 4,000 American women have died from pregnancy and child bearing.

But the real human suffering is not in deaths but in morbidity, complications of pregnancy, and childbearing today remains a very complex process. Again, the most recent data from the CDC in Atlanta are on the screen. Forty-three percent of all U.S. women have one or more complications during the hospitalization at which they deliver, such as hemorrhage, infection, obstetrical tears. Indeed, one in four American women are hospitalized at least once during the pregnancy but before delivery for

complications of the pregnancy, such as threatened labor, preeclampsia, urinary tract infection.

Now, if you multiply these percents times the millions of pregnancies every year in the U.S., you can see how huge is this burden of suffering, and many of these complications are severe and long lasting.

Now, in medicine we oftentimes have to make difficult decisions between competing risks and benefits. Not so here, not so. Seldom in medicine do we see the scale so forcibly tipped and permanently tipped in favor of benefit, but let's consider yet another dimension of the problem of unintended pregnancy in America, and that is induced abortion.

Induced abortion is prima facie evidence of unwontedness, and despite impressive gains in recent years, we still have far too many abortions in America. As you know, our abortion rates are much higher than in other industrialized nations. Nearly a million abortions reported to the CDC each year. Two measures commonly indicate how frequent is abortion in a population, the abortion ratio and the

abortion rate.

The ratio is the number of abortions per 1,000 live births. The rate is number of abortions per 1,000 women of reproductive age, and again, the most recent data from the CDC indicate that for every four live births in America there is one induced abortion, and indeed, two percent, one in 50 American women of reproductive age have an abortion every year.

And here emergency contraception over the counter has an extraordinary role to play by reducing the need for induced abortion, and that's a goal around which there should be broad consensus in America, and this is already happening.

According to the most recent data from the Alan Guttmacher Institute, in the year 2000, despite limited use of emergency contraception, it has averted over 50,000 abortions that would have taken place without its use.

Think what we can do together with easier, wider access to this safe product.

An old concern about emergency contraception and easy access to it was that this

would in some way sabotage or undermine ongoing traditional contraception. I heard this discussed just an hour ago on CNN.

There are studies around the world refuting this. It doesn't happen. Moreover, a study done by the World Health Organization looking at frequent repeat use of the product indicated that it would disrupt normal menstrual cycling, which itself would deter women from using it in this fashion.

As you've heard from the prior two speakers, over-the-counter levonorgestrel easily fulfills the three criteria outlined in the Durham-Humphrey Drug Amendment Act of 1951. There are no outstanding medical issues.

Speaking as a gynecologist, my patients have told me that one of the most important benefits to them, difficult to measure, is peace of mind. Unprotected intercourse can cause terrible anguish that may list for weeks to months occasioned by unplanned sex, forced sex or a contraceptive mishap, such as forgotten pills or a torn condom.

I would remind all of us here today that

this discussion is ultimately not about a steroid molecule. It is about women, women at a time of acute and often terrible crisis in their lives. Emergency contraception can help by reducing unintended pregnancies, induced abortions, and medical suffering.

In conclusion, today the FDA has an extraordinary opportunity to advance women's health in America by removing needless gratuitous obstacles that stand between women and safe medicine. I would ask you to consider the alternative.

If we allow these obstacles to stand, if access remains limited, we will be indirectly causing unintended pregnancies, induced abortions, and needless human suffering. The public health and the medical evidence is clear and incontrovertible. The choice before us today should be equally clear. Over-the-counter emergency contraception is good medicine. It is scientific medicine. It is compassionate medicine, and it is medicine that women deserve.

Thank you.

DR. BEN-MAIMON: Thank you, Dr. Grimes.

I'm going to try and put some background

or some sort of meat on the bones and talk a little bit about what we're seeing happening in the United States with regard to pregnancy rates, teenage pregnancy, and abortion, and then go into some of the issues surrounding emergency contraception.

You can see here the white line is the U.S., women 15 to 44, and the pregnancy rate since 1990, and you can see that the line is decreasing, but somewhat stable.

What's really interesting is the pink line, which are women 15 to 19, which is decreasing disproportionately to the rest of the population. The same thing occurs when you look at abortion rates since 1990. You see the line here where abortions that were decreasing now seem to be somewhat stable, but look at the pink line in women 15 to 19, which is going down. This obviously we would all agree is a very good thing and a trend we'd like to see continue.

Here are the percentages of women using various contraceptives in contracepting women. These are 15 to 19 year olds. These are 20 to 24 year olds, and what you see here is that since 1982 the trend in

OC use has been going down, but there has been a corresponding trend increasing in condom use.

Here in 20 to 24 year olds it tends to be more flat, but again, the increased use of condoms is demonstrated in these women, and clearly, this is probably a result of the better understanding and the greater awareness of sexually transmitted infections and the need to use a barrier method in order to prevent the transmission of those infections.

What's interesting here when you look at contracepting women 15 to 19, 20 to 24, 25 to 34, and then 35 to 44 is that young women tend to prefer reversible forms of birth control, such as oral contraceptives and condoms, whereas older women tend to prefer sterilization and more permanent forms of birth control, not something that's terribly unexpected, but clearly an interesting piece of information.

Again, unplanned pregnancies are a major health problem in this country as you've heard from both speakers and the FDA. Education and awareness programs seem to be working, but clearly, we need to

do more in order to decrease the incidence of unintended pregnancies and abortion even further.

Despite these programs, there are over three million unintended pregnancies a year, half of them ending in abortion. Again, 50 percent of these unintended pregnancies could be prevented by greater use of emergency contraception.

It's very important to remember that of women who present for abortion, only 1.3 percent of those women have used emergency contraception, and as Dr. Grimes said, this is really the ultimate in unwanted pregnancy. They choose to abort the baby, and so clearly, if only 1.3 percent of them are using emergency contraception, we have a long way to go in increasing access and availability and awareness, and we believe awareness of and access to emergency contraception needs to be enhanced in order to impact this major health care problem that we're facing.

We believe that Plan B is safe and effective for over-the-counter use, and we believe the data supports that. Although pharmacy access programs may increase availability, they create new barriers

that need to be dealt with by women who seek them.

And so I'd like to spend a couple of minutes talking about pharmacy access and what is going on with regard to prescriptions in this country for Plan B, and then I'm going to talk a little bit about our CARE Program, which we hope will help to increase awareness and availability, and it's clearly designed to do so.

This is the prescription data from the United States. It's Plan B, and it's retail pharmacies only, and what it shows is at this point there are about 20,000 prescriptions a month for Plan B.

This is California, which is the pharmacy access state. What's important here is that the legislation was actually implemented in January 2002, and you can see that with the implementation of that program, there was an increase in the script writing for Plan B.

This is Washington State, which is flatter, still increasing, but flatter, and their program started in 1997, and so access has been around

for quite a bit longer.

There are five pharmacy access states: Washington, California, Alaska, New Mexico, and Hawaii. These are newer so I won't be discussing those, because those states are actually too new to identify what is really happening, but I'm going to talk a little bit about Washington and California.

It's important to note that the legislation in Washington actually provided for pharmacy access, and pharmacy access means access to Plan B without a prescription through a pharmacist. So the pharmacist has to write a protocol, file it with the State Board of Pharmacy, and then they can participate in the pharmacy access programs, and there are certain educational requirements as well.

What you see in Washington State -- and this is the time line -- is that there are about 2,000 scripts a month up from 1,000 over maybe three years ago, but what I think is really important to note is that in a state where there has been pharmacy access for emergency contraception since 1997, there are only 26 percent of pharmacies participate, and only 23

percent of pharmacists. It takes initiative to participate in these trials. The pharmacists have to be trained. They have to apply. They have to want to participate, and so it's not just so straightforward that women can walk in and obtain emergency contraception.

California. One of the things I think that has increased use of Plan B in California is the fact that they had a huge media campaign. They had a huge campaign to try and increase awareness of the product, and they targeted about ten million consumers and health care professionals. Over 900,000 women were with print material; a million women and men through paid advertising; 70,000 health care providers through print material; and approximately eight million people through free media.

What did this result in? Again, the legislation went into effect in 2002, January. So it is essentially two years. Only 14 percent pharmacies and pharmacists participate.

So, again, in a state as large as California, finding emergency contraception without a

prescription is still a significant challenge.

What does that mean for the United States? Well, we've got five states. There's 45 left to go. More than 200,000 pharmacists are throughout the United States, 53,000 pharmacies. The pharmacists have to be recruited for pharmacy access, and so this in and of itself is a huge challenge and really limits the ability of pharmacy access to act as the mechanism to increase availability.

Let's look at barriers again. Clearly, here there's the barrier of getting the pharmacists and the states to participate, but let's say we can do that. There's another barrier, and that is that these programs require protocols. Women have to walk into a pharmacy, talk to the pharmacist, answer questions, and qualify for pharmacy access and for emergency contraception.

Many of you can put yourself in the position of a woman, and I don't know if your pharmacies are like my pharmacies, but there really aren't any areas where I could hold a private conversation with my pharmacist and answer these types

of questions in a way that would be comfortable for me.

And so clearly, the need to consult with the pharmacist, at least be interviewed by the pharmacist, not and ask questions, but be interviewed and meet certain criteria, could act as a significant barrier for women to seek emergency contraception through pharmacy access.

So again, although Plan B is safe and effective, access and availability are still too limited to have the kind of effect that we believe it can on the incidence and rates of unintended pregnancy.

And with that I'll switch a little bit to the CARE Program. The CARE Program is designed to provide and encourage awareness and increase awareness of women that emergency contraception exist; that they can get it; how they should use it; and in what context it fits in overall reproductive health management.

And it is also intended to increase availability so that when they do need it, they can

seek it and they can find it and they can get it. I'm going to take a minute and hand out these packages. You can pass them around.

These packages are the actual packages that we're proposing and are part of the supplemental NDA. You can see that there's an outer package. Feel free to open them. There's an outer package, and in it is a smaller package that opens up and actually has the directions for use. The outer package has the drug facts section on the back, and that's what the women would see when they went into the pharmacy.

Included in the package would be information on routine forms of contraception, as well as sexually transmitted infections. There would also be reference to a hotline which I'm going to talk about in a minute and a Web site, and there's also a data card which I'll talk about in a couple of minutes as well.

But feel free to open them, look at them, and pass them around.

The need for accessible emergency contraception is great, but clearly, awareness is low

and availability is limited. The program is designed to increase awareness through education. Programs will be comprehensive in nature, and what we mean by that is we will include information on what we call Plan A: abstinence, family planning, and routine forms of birth control.

The name Plan B was not just a marketing tool. The name Plan B was chosen in order to communicate to women that this is Plan B. Plan A is abstinence, family planning, and routine forms of birth control. Those are the preferred mechanisms to prevent pregnancy.

But when Plan A fails, Plan B is available. The target audience will be consumers, physicians, physicians' assistants, nurse practitioners and pharmacists.

The second part is distribution and availability, and I'm going to talk about that a little later, but the intent of OTC distribution is to minimize delay so that we can maximize the earlier use of the product and lower the barriers in order to maximize appropriate use and, finally, to insure

availability.

Again, the communication objectives. Plan A is abstinence, family planning and routine forms of birth control, and I can't reiterate enough how committed we are to helping to support that message.

Plan B is used when a woman has concerns that Plan A hasn't worked for whatever reason. Plan B is not a replacement for routine forms of birth control. Plan B does not treat or prevent sexually transmitted diseases, and follow-up with a health care practitioner is strongly recommended.

What is the problem with regard to awareness and education? Only 43 percent of women know that EC is available in the United States. Only six percent have used it, and one of the most important statistics that we have here today is that only 1.3 percent of women who present for induced abortion have used emergency contraception.

What we're intending to do with our program is try and utilize all of the tools that we have available to us. Barr has a sales force of about 250 representatives that visit approximately 30,000

physicians throughout the country. We intend to distribute informational brochures to those physicians through our sales force so that women while sitting in a waiting room or waiting in an exam room can read about emergency contraception, understand what's going on, and talk to their doctors or their nurse practitioner if they have any questions before this happens.

Again, these materials will also hopefully stimulate discussions with regard to routine forms of birth control and family planning issues.

Educational brochures will also be available at the point of purchase, will be providing display units that can be put out at pharmacies. There will be no trial offers, coupons or samples.

We will have print and radio ads which will include and be mostly designed as public service announcements and informational materials that talk about diagnosis, need, and responsible use. And so the program is really targeted at increasing awareness, making women understand how and where to get emergency contraception and how and when to use

it.

This is the label. You have it in front of you so I'm just going to flip through it in an effort to save some time.

There is a card in the package, and women will be able to record the time of the first dose and then calculate the time of the second dose, and of course, it encourages them to take it as soon as possible.

It also refers them to our hotline, as well as to the Web site.

The toll free number will be staffed by a health care professional 24 hours a day seven days a week. So when women need and choose to use emergency contraception, they will be able to call if they need help or if they have questions in order to get additional information.

There will also be a Web site with links for health care practitioners, and we will encourage women if they have any further questions to follow up with their health care practitioner.

From the standpoint of professional

education, and I think this is also important because clearly OB-GYNs understand about emergency contraception, but there are many doctors out there who are not as knowledgeable and so we will be advertising in professional journals. We will provide continuing education at medical meetings and in relevant settings. We will work with pharmacists through our national account managers, pharmacy journals, and again provide continuing education through state boards of pharmacies at their annual meetings, as well as major pharmacy meetings.

The problem of distribution. Again, this is really a two-part issue. It's awareness and education, but it's also distribution and availability and access. Only 35 percent of pharmacies in Pennsylvania were able to get Plan B or emergency contraception within 24 hours.

In Albuquerque, New Mexico, which is a pharmacy access state, 89 percent of pharmacies did not have Plan B, and 53 percent of them could not access it within 24 hours. Clearly, the clock is ticking.

Again, although the need is great, availability is still very limited. We are proposing to sell to wholesalers, clinics, or retain chains and stores with valid pharmacy licenses or valid wholesale licenses.

Again, we will be supplying display units for pharmacies to put out with informational materials. We will continue to provide Plan B at a discount to clinics so that all women can have access to it, and again, I'm sure you remember from the briefing package we committed to recommending that Plan B be kept either behind the counter or in view of the pharmacies.

We are very comfortable that Plan B is safe and effective for over-the-counter use. We are very comfortable that it could be sold completely over the counter, but we recognize that there are issues surrounding this product and concerns that need to be addressed, and so we're very anxious to hear what the committee thinks with regard to the placement of these products in pharmacies, and of course, if it's recommended that we recommend keeping it behind the

counter, we will take that into consideration and discuss that with the agency.

CARE is intended to encourage appropriate use of Plan B through professional and consumer education. It's intended to insure awareness that Plan B is conveniently available and to teach women when and how to get it. It's intended to reinforce that it is safe and effective with appropriate packaging and labeling, which you see in front of you. And finally, we will have monitoring programs to see whether or not the program is working and what modifications need to be made. As we go through time the needs may change, and clearly, we will be working on that as we go.

Unplanned pregnancies are a major health care problem in the United States. Over three million unintended pregnancies occur each year. With typical use, women using condoms, 15 percent of them will become pregnant each year, and eight percent of women using oral contraceptives will become pregnant.

There are approximately 800,000 unintended pregnancies in teenagers. In 2002, 215,000 women in

the United States were the victims of rape or sexual assault. Half of the unintended pregnancies result in abortion, and again, it's estimated that up to 50 percent of these unintended pregnancies could be prevented with the use of emergency contraception.

Plan B will insure that for those who need EC, there will be convenient availability and responsible education. Making this product available over the counter will decrease the barriers and increase access, hopefully resulting in a reduction of the number of unintended pregnancies.

Plan B has a demonstrated safety profile and is suitable for over-the-counter use. Early use is absolutely critical to maximizing effect. The prescription requirement presents barriers that delay the chance for early use of emergency contraception. Plan B meets an unmet medical need, and the Plan B CARE Program insures responsible and appropriate education and distribution.

Plan B for OTC use, along with the CARE Program, will provide important benefits to the consumer. It will enhance availability and minimize

delay while maximizing efficacy, and ultimately it will reduce the number of unintended pregnancies, a major health care problem in this country.

With that, thank you very much.

CHAIRMAN CANTILENA: Okay. Thank you.

We now have time for questions from the committee to the sponsor, and I would ask the committee members to signal me so they can be called on. We will not allow cross-talk, and we would ask also that your questions at this point be focused and specific in terms of exactly, you know, the sponsor, you should not be asking any questions of the FDA because you'll have an opportunity to do that later this morning.

So questions from the committee. Dr. Benowitz.

DR. BENOWITZ: I have a couple of pharmacologic questions. The first one is the way this drug is supposed to be given is one dose based at 12 hours. The drug has got a long half-life. There certainly are reasons to think that 12 hours is not important.

One question is whether even having two doses is important, and the second one -- and I know it's not part of this proposal -- but in reading the background material it seemed striking that 1.5 milligrams in a single dose was just as effective and no more toxic and certainly easier to comply with.

And so one question is about the dosing issues, and then I've also got a second question.

DR. BEN-MAIMON: The variations in dose have been studies in other parts of the world, and WHO has actually done some studies looking at single one and a half milligram doses. The issue really is that what's approved today is one dose within 72 hours followed by a second dose 12 hours later.

The safety and efficacy of that product is well documented, and so what we're seeking today is to move the prescription to OTC for that regimen, recognizing that maybe in the future there would be a reason to develop alternate dosing regimens.

DR. BENOWITZ: And what about the first part? What if someone doesn't take a second dose? Will it still work?

DR. BEN-MAIMON: Well, there is not a lot of data on 1.75 milligram dose, but clearly women do take the second dose. I mean, the actual use study demonstrates that, and there's a failure rate for all of these products.

I mean, this is not a foolproof method to prevent pregnancy. It prevents most or a lot of the pregnancies, but it doesn't prevent all pregnancies.

DR. BENOWITZ: Okay, and then a second question. The efficacy data that you showed were quite striking in that taken within 24 hours, the pregnancy rate was .4 percent. On the third day it was 2.7 percent.

The labeling really doesn't make that point very well. It says take as soon as possible, but it clearly doesn't tell a woman that you could have a six or sevenfold difference in efficacy rate if you take it within 24 hours versus 72 hours, and why have you not really emphasized the importance of 24 hours?

DR. BEN-MAIMON: Well, I think we have emphasized the importance of taking it as soon as

possible. You can see from what's happening here it's not possible all the time even to get it within 24 hours, and so as soon as possible is, I think, as much as we can say.

In addition, we don't want to discourage women that after the first 24 hours have passed, you know, you might as well give up because it is clearly effective. As you get out even past 72 hours, there's some data to support, as Dr. Dickerson said, there's some data to support that it may be effective out as long as five days.

But clearly, we want women to take it as soon as possible, but we also want them to take it at 24 to 48 and 48 to 72 hours, as well, and not just throw up their hands and give up.

CHAIRMAN CANTILENA: Okay. Thank you.

Over here, Dr. Macones and then Dr. Hewitt.

DR. MACONES: You mentioned about some post marketing information on rates of ectopic pregnancy. I was wondering if you'd just expand on that a little bit more because the numbers are fairly

small even from the clinical trials that you've done.

DR. BEN-MAIMON: Okay. Can I have Slide -- yeah.

What you see here are the exposure numbers throughout the world. There are over six million women who have been exposed to Plan B throughout the world. Total pregnancies reported are 340, but again, pregnancies are not likely -- remember this is pharamacovigilance data. This is not data from clinical trials. So women are not reporting every normal pregnancy clearly.

There have only been 21 ectopic pregnancies, and when you do the calculation based on the number of uses, the expected number of pregnancies, you would expect to have with a two percent risk 585. So there is significantly fewer reported ectopic pregnancies.

Again, we recognize, again, these are pharmacovigilance data. So they have their limitations, but you get similar numbers when you look at the clinical trials, and although the clinical trials are small, you still have over 7,000 women in

133 pregnancies. So they're not negligible, and those are clearly pregnancies that were followed up.

So I think if you combine this data alongside the data that was presented from the clinical trials, there really is no reason to expect an increase. There is no data to suggest that there's an increased incidence of ectopic pregnancy.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Hewitt. and then Dr. Wood.

DR. HEWITT: Yes, I have a couple questions. The first one is about when patients call in on the hotline or attend the Web site and how their questions will be answered. The first question has to do with multiple acts of intercourse and taking multiple doses of emergency contraception.

I'm thinking specifically if a patient has missed a couple of birth control pills in a pill pack and has not had contraception for an extended period of time. How will she be counseled when she calls in over the phone?

And then secondly, when she calls in with questions about dosing intervals, will they be giving

any information on options with dosing of the two emergency contraceptive pills in terms of the 12-hour window? Will they be given options of taking both pills at once?

How will they be counseled with those phone calls? I know when I counsel patients I tell them, you know, you don't need to set an alarm clock for 3:00 a.m. to get up and take your second dose, but how will those kind of questions be answered?

And then my second question has to do with communicating this information to and supporting team use. I know that literacy studies were not done on women less than 18. Do we have any information besides what you gave about how they answered the questions to the 11 points you were trying to convey?

Will any of the materials be sort of teen friendly or be developed specifically to reach younger women?

DR. BEN-MAIMON: Your first question about counseling, and if I don't answer it all, please feel free to come back because I may have missed some of it.

We will have trained professionals, first of all, health care professionals, women, you know, with nursing degrees or pharmacy degrees staffing the phones. Those people will be have a script, and they will counsel women on the different -- we'll have all the different scenarios laid out, and they will counsel women based on a script that will be designed with physicians in order to tell women what to do.

I think if women have missed three or more birth control pills, they would be instructed to take Plan B and to use a routine form of birth control at least for the first week, depending upon where they were in their cycle and what the labeling says for oral contraceptives.

And of course, if there's any concerns, it would be recommended that they follow up with a health care practitioners.

But those scripts would be designed with physicians and would be provided and these people would be trained in order to deal with those types of questions.

With regard to teens, we all want our

teenagers to refrain from sexual activity prematurely. I don't think any of us want our teenagers to be sexually active before they are comfortable and should be. And clearly we will be reinforcing the messages of abstinence and all of that, but it is clear that there are 800,000 pregnancies in teenagers every year, and so we really do have to deal with that issue.

The label comprehension study, as you saw, had women in it from 12 to 50, and there were actually a significant number of teenagers 12 to 16 years of age in that study, and I think we presented the objectives, and we can put that graph up again. It is number 24, please.

And you can see here that these are the objectives. The 12 to 16 year olds scored actually quite well for the vast majority of the objectives, and so the materials seem to be pretty appropriate for them, and they do seem to understand and be able to comprehend.

DR. HEWITT: And what about my middle question about the dosing interval? You know, if a patient literally says -- you know, I mean, are they

going to be explained any leeway on dosing the second interval, or do you anticipate the scripted response will be 12 hours, period? Are you able to answer that question at this point?

DR. BEN-MAIMON: Yeah, I think it would be 12 hours. I think that's what the labeling says. That's what the data suggests. This is a product that will be taken once. So we're not talking about having to wake up in the middle of the night for, you know, the next week and a half or six weeks.

I think for one time we would recommend that people take it at 12 hours, and that the 12 hours, if it occurs in the middle of the night, they get up and they take their dose.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Wood.

DR. WOOD: Yeah, I have two questions that relate, I guess, to access. The first one relates to the paper that's Tab 8 in our briefing book from Anna Glasier and David Baird that was published in the New England Journal, and they encouraged the patients or, in fact, they provided patients with the equivalent of

Plan B to keep in their bathroom cabinet, and that seems to me the obvious way to go. I mean, there's not much point in telling people to buy a fire extinguisher once the fire starts burning. You tell them to get a fire extinguisher and keep it in their kitchen.

And similarly, we've had a lot of medical experience now with defibrillators that the effects of defibrillators are much more effective if they're on site and readily available for use.

So my first question relates to that. Are you going to encourage in the promotion material that people obtain the Plan B and have it available in their bathroom cabinets and for use in the case of an emergency, and if not, why not?

DR. BEN-MAIMON: Well, I think that there is no question that the data suggests that women who have emergency contraception use it more frequently.

There's also no data to suggest that women who have emergency contraception have more unprotected sex. It's just that when they have unprotected sex, they use the product because it's available to them.

And so the materials, I think, will be designed to make sure that women are aware of how to access and how to get emergency contraception. I don't think we've contemplated having specific statements in there that say, you know, "Make sure you have one of these at home."

Again, there's situations of expiration dating and other things that have to be taken into consideration, but of course, we can consider that.

DR. WOOD: My second question related to your comment near the end of your presentation about making it behind the counter. That seemed to me totally counterintuitive, and that seemed to me to raise all of the access issues that you quite eloquently addressed earlier.

So it would seem to me that that would totally obviate the benefits of making Plan B over the counter, and I can't imagine how that would be advantageous.

DR. BEN-MAIMON: We appreciate your comments, and that's one of the reasons we raised it, because we think there are opinions both ways, but we

are concerned about putting it behind the counter simply because of the issue of barriers, and that's why we're interested in hearing what the panel thought about that.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Trussell and then Dr. Montgomery Rice.

DR. TRUSSELL: I want to follow up on Dr. Wood's question.

In the pharmacies in my hometown now, condoms, spermacides, KY jelly are all locked in cabinets that can be opened only by the pharmacist, and when I've asked repeatedly why they do this, it's because they were being stolen blind.

(Laughter.)

DR. TRUSSELL: So my question is in your conversation with the pharmacy chains, do you have an indication that this product is going to also be locked in that cabinet? Because my pharmacists are certainly going to lock it in their cabinet.

DR. BEN-MAIMON: Well, what we are proposing, there's a thing called a Planigram, which is the pharmacies lay out where they have all of these

products, and you know, they figure out where they're going to place them.

Our recommendation to the pharmacists will be that it be placed in the female health care sections along with pregnancy kits and things like that, which are not locked behind cabinets.

DR. TRUSSELL: In my pharmacies, they are locked behind cabinet.

DR. BEN-MAIMON: Oh, I don't know where you live, Dr. Trussell.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Trussell.

(Laughter.)

CHAIRMAN CANTILENA: You should consider moving to another neighborhood.

(Laughter.)

CHAIRMAN CANTILENA: Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I thought in the literature that I read that you were removing the vaginal bleeding from contraindication to warning, but when I looked at the package on the back you do not have vaginal bleeding in the warning section. You

actually have it under the side effects, which if I was a lay person I would think that that means I was going to have vaginal bleeding after unintended -- unintended vaginal bleeding after taking the medication.

I think that should be clarified because it wasn't clear to me.

DR. BEN-MAIMON: I may be mistaken. I thought it was in both, but it's conceivable that I'm mistaken.

DR. MONTGOMERY RICE: I don't see it on the back.

DR. BEN-MAIMON: Okay. Well, we'll check.

DR. MONTGOMERY RICE: And I think that needs to be clarified.

The other thing that I'm concerned about is that you roll out this wonderful program called the CARE Program and you say you're not going to give out any coupons, samples, or rebates, and so I'm concerned about the lower socioeconomic patient who really requires this medication and the reason the patient may not be taking a reliable contraceptive is because

she can't afford oral contraceptive pills.

So I'm wondering what's the reasoning for not having some type of assistance program with obtaining the medication.

DR. BEN-MAIMON: I would like to make a distinction between coupon samples and an assistance program. An assistance program I don't think is something that we've considered. I think we would consider it.

We will be continuing to supply it to clinics at a discount. So it will continue to be available at clinics for women who source it there and who are used to using clinics as access for their medical care.

But I don't want to imply that samples and coupons are related to an assistance program, and that's not something that we've considered, but we would be willing to.

CHAIRMAN CANTILENA: Okay. Thank you. Thank you.

We actually are out of time. So what I'd like to do is ask you to hold your questions until

this afternoon. We will have the opportunity to ask questions of the sponsor after lunch as well.

And what we'd like to do now is to pause for 15 minutes. We'll take a 15-minute break, and we'll come back with the FDA.

Thank you.

(Whereupon, the foregoing matter went off the record at 9:50 a.m. and went back on the record at 10:09 a.m.)

CHAIRMAN CANTILENA: It's now time for the FDA presentations, and our first speaker for the FDA will be Dr. Davis.

Dr. Davis.

DR. DAVIS: Thank you.

Good morning. My name is Dan Davis, and I'm a medical officer in the Division of Reproductive and Urologic Drugs.

I did the primary clinical review for efficacy and safety for the original Plan B submission and have followed the sponsor's periodic safety reports and the medical literature on emergency contraception since the approval of Plan B as a

prescription drug in July of '99. My responsibility for the current Plan B submission is to evaluate any safety concerns relative to the requested change to a nonprescription status.

The topics to be presented are in the following order: the points to consider for the switch from prescription to nonprescription status; marketing data on U.S. and global use, as well as distribution patterns and availability of levonorgestrel for emergency contraception, which I will often refer to simply as EC throughout my talk; the sponsor's safety data from both the original submission and the subsequent post marketing data; findings from the current FDA safety review; the potential for misuse and abuse; contraindications; and I will close with a summary of the FDA safety conclusions for levonorgestrel.

Occasionally I may mention the term "postcoital contraception," which is a more routine primary method of contraception for women used, taken after intercourse. The topic today is really emergency contraception, which is single use, but a

lot of our data for safety comes from original studies dealing with postcoital contraception.

The prescriptions to nonprescription, which has already been carefully discussed by Dr. Rosebraugh and the sponsor, I will concentrate on the first two items here, namely, an acceptable margin of safety and the potential for misuse and abuse.

Dr. Chen will discuss whether the product was safe during the actual use study, and finally, the committee members here will be asked to discuss the benefits relative to risk after all of our morning speakers have presented.

The sponsor's exposure data comes from many different sources, but first of all, I want to just remind people that Plan B is levonorgestrel 0.75 milligrams taken times two doses. The sponsor estimates the U.S. exposure at 2.4 million uses since the approval of Plan B in 1999. Worldwide, emergency contraception pills are available in 101 countries.

The levonorgestrel products in the U.K. and France are identical to Plan B. Exposure is estimated to be at 2.1 million in the U.K. and 1.8

million in France.

Most recent 12-month data that's available from Canada shows 72,000 uses in a one-year period of time.

The above exposure data clearly shows that levonorgestrel for EC has been used by several million women in at least four countries in the recent years.

The distribution patterns show at least four methods of availability. Most common is a routine prescription for EC as needed. Sixty-eight countries, including the U.S. have EC availability by prescription.

Advanced provision of a written prescription or the actual product is becoming more common and is promoted worldwide by many organizations and clinics. Globally EC is available directly from a pharmacist in 33 countries, and as discussed earlier, in five states.

Barr has already covered the availability in the U.S. The largest and longest program is obviously from the State of Washington. The California pilot program started in the year 2000, and

by January of 2002, the California legislature passed a law allowing a statewide effort as outlined.

The other three states are Alaska, New Mexico and Hawaii.

The fourth method availability is that EC pills are truly available over the counter in Sweden and Norway. Clinical trial data are considered to be the gold standard for safety data because trials are often use strict protocols, control arms, added visits, more safety monitoring, and good data collection.

The original Plan B submission contains safety data from several clinical sources. The pivotal blinded and comparative World Health Organization Trial included 1,955 women. The primary data sets were submitted with the NDA application and reviewed by our reproductive division, basically by myself, and for both safety and efficacy.

Levonorgestrel alone in that study was compared to the m ore traditional Yuzpe regimen, which is a combination of levonorgestrel and an estrogen.

From three ongoing World Health

Organization trials, plus some introductory trials of prescription levonorgestrel in three European countries for use as EC, and the pivotal WHO large trial, no serious events commonly called SAEs had been reported by the approval date for Plan B.

From the literature review, more than 15,000 women from 29 countries in clinical trials using various doses of levonorgestrel for either EC or postcoital contraception had been studied. The data showed that levonorgestrel taken for contraception after intercourse was well tolerated.

This data from the extensive review did not uncover any deaths, cardiovascular problems, thromboembolic events, or serious adverse events. Those adverse events that were reported were consistent across all studies and reflected the AEs that are listed in the current Plan B label.

In summary, the FDA review of the sponsor's clinical trial safety data did not find any safety signals of concern.

We next rely on post marketing data which has been obtained since the approval of Plan B. In

contrast to clinical trial data, it is important to note the limitations of post marketing data. They're outlined here.

The use or exposure data is often estimated. The likelihood of reporting adverse events may be greater or lesser, depending on the nature of the event.

Third, we know that there's considerable under reporting of adverse events.

And fourth, many of the post marketing AE reports lack complete clinical information.

There are many different post marketing sources of safety data, but overlapping of the reports often makes it difficult to interpret the data. The sponsor provided different sources of post marketing data.

First were the FDA required periodic safety reports covering from the time of approval up till January of 2003. This contained 345 reports. Reported most often were 123 pregnancies and 64 cases of bleeding. Most of the reported events were mild and short term. All were labeled events, and there

were no reports of transfusions, SAEs or deaths.

Many of the reports actually did come from European sources, even though reported to our periodic safety update to the FDA.

The global safety databases included national pharmacovigilance agencies in key European countries and Canada, the World Health Organization Drug Monitoring Program, reports from the manufacturer of Plan B, and several other databases.

From these various global databases there were no reported deaths, no strokes or thromboembolic events. There was one case reported in France in a 22 year old woman who was hospitalized with phlebitis, but did not have any further problems.

In summary, based on all of the safety data from clinical trials involving 15,000 women and from several post marketing data sources worldwide, the sponsor's conclusion is that Plan B is an appropriate candidate for a switch to a nonprescription status.

Our division requested a consultation from the FDA Office of Drug Safety with a focus on serious

adverse events and ectopic pregnancies. The consultation reviewed the FDA adverse event reporting system, commonly called AERS, A-E-R-S, and data from the U.K. In the AERS database there were 116 unduplicated cases, and 60 percent of these were for nonserious labeled events, such as vaginal bleeding, pregnancy, abdominal cramps or pain, and nausea and vomiting.

Many of the reports had incomplete information and are, therefore, hard to interpret.

From this data set there were no deaths, serious cardiovascular or thromboembolic events or transfusions reported to AERS from any country. As already noted, we have over four million uses of levonorgestrel from the U.S. and the U.K. since 1999, and this data is primarily U.S. and U.K. data.

There were ten cases of an allergic reaction that were reported. Three were from the United States. Most were minor, although two women did have some difficulty breathing. Nobody was hospitalized.

Under fetal risk, there are eight reports

that included five cases of a spontaneous or inevitable abortion, and three cases with congenital anomalies, all reported from Europe. This number of cases is well below what we would anticipate, given the spontaneous abortion rate of ten to 15 percent of all pregnancies and the congenital anomaly rate of 0.85 percent.

The other finding on the AERS database was ectopic pregnancy. There were 28 reported cases. None were from the United States, and there were no deaths. Because the incidence of ectopics is dependent entirely on the total number of reported pregnancies relative to the number of ectopics, we like to use a database where the number of ectopics and total pregnancies is as reliable as possible. For this type of information we look at randomized clinical trials as mentioned earlier.

From the six large randomized clinical trials involving the 7,889 women, we see that there were the two ectopics and a total of 135 pregnancies or an incidence of 1.5 percent. As already pointed out by Barr Pharmaceutical, this is the same incidence

as we would expect in the general population. So it does not raise an issue that ectopics should be of concern.

This slide is a little bit busy, but of all of the potential misuse and abuse problems, we considered overdose, higher doses, repeat use, and use in pregnancy, and incorrect dosing.

For overdose, there were no reports in the literature or safety databases of an overdose. Overdose is also unlikely with the expected cost of Plan B.

The second bullet really should be for higher doses, and the best safety data for exposure to higher or repeated doses comes from European trials in the 1970s and '80s, in which levonorgestrel was used for regular postcoital contraception. In these trials levonorgestrel .75 milligrams was used up to eight times per month or total doses of 2.25 milligrams within 24 hours were used and repeated as needed, and a single dose of .4 milligrams taken on average eight to nine times per month for an average of nine consecutive months were also used.

From this database, again, we do not see any safety signals with problems with serious adverse events, deaths, or hospitalizations.

Repeat use, there are many, many different studies that could be quoted. I elected to talk about the Rowlands study from the United Kingdom. The database was over 15,000 medical records of women who did use EC once. The age range was 14 to 29, and these women were followed for four years.

Rowlands found that repeat EC use was uncommon per year or over a four-year period of time. For example, only three percent of the women, 15,000 women used EC twice in the four-year period of time. One percent used EC three times in the four-year period, and .8 percent used EC greater than three times over a four-year period of time.

We also are aware of this one-year study by Glasier and Baird of 1,000 women in Scotland, where EC use was used more often with advanced provision, but for the women using the product more than once in the entire year, 11 percent of the women with advanced provision used EC more than once, and 13 percent of

those without advanced provision used EC more than once.

Use during pregnancy shows no clear evidence that inadvertent use of levonorgestrel during a pregnancy will result in abortion or cause fetal problems.

For incorrect dosing, in other words, not using the product strictly according to the label, there are recently published randomized clinical trials that report on a single dose of 1.5 milligrams levonorgestrel being safe and effective. The second dose can be taken later than the labeled 12-hour dose, and we do have information on the first dose being started between 72 and 120 hours.

I'm not going to discuss these further because that's really not the point of our meeting today.

Contraindications from the prescription Plan B label has already been addressed somewhat. The current label for prescription lists three contraindications based solely on the class label for progestin only oral contraceptive pills, which are

taken daily for routine contraception. The prescription label clearly states that it is unknown whether these same conditions apply to the Plan B regimen.

Hypersensitivity to any component of Plan B is certainly a contraindication and should be listed. It is a rare event, and there have been no reports of death or hospitalization due to allergy.

Known or suspected pregnancy is not a contraindication. It is listed primarily because the product will not work if the user is already pregnant, and this is really not a safety issue.

The sponsor has talked about removing the undiagnosed abnormal genital bleeding from the label. Our division is in general agreement with that principle, but we still do not have the final label and the final approval of the product.

So our evidence of safety comes from many different sources: the original NDA trial data, which we have discussed; and since that time, there have been four additional published randomized clinical trials enrolling 6,503 women in levonorgestrel only

arms and using the same total dose as Plan B.

This gold standard for drug safety and efficacy had the following findings: no reported deaths; no vascular events; no thromboembolic events; and as mentioned earlier, there were two ectopics in 135 pregnancies, which is the same incidence that would be normally expected.

Post marketing data since July of '99 shows the following. There has been obvious extensive EC exposure in the U.S., U.K., and France, and over six million estimated uses. There have been no deaths, heart attacks, strokes, or thromboembolic events reported with EC use in the medical literature or post marketing surveillance.

There's only one report of phlebitis in the 22 year old woman from France. No reports of overdose, and I found no evidence for abuse or misuse.

Of the eight fetal AEs reported in the FDA AERS database, there were the three congenital anomalies and five miscarriages. This is very low compared to the background rate as mentioned earlier.

We have reviewed the data submitted by the

sponsor in the current NDA application. We have done our own review of randomized clinical trials, the voluminous medical literature on EC, the FDA's AERS database, and other databases.

Levonorgestrel has been used extensively worldwide for over 35 years, in combination oral contraceptives, levonorgestrel oral contraceptives and for postcoital contraception, and EC.

Plan B, with a total dose of 1.5 milligrams levonorgestrel, has a safety profile that includes no deaths, strokes or thromboembolic events. Single doses up to 1.5 milligrams, repeated doses of .4 milligrams up to 25 months, and repeated doses up to 2.25 milligrams in a 24-hour period of time have been studied.

There is a low potential for misuse and abuse. The safety risks are very limited. We believe that allergy is the only contraindication which is rarely seen, and there are no reported deaths or hospitalizations.

Finally, there are no clear risks to a pregnancy or the fetus that have been demonstrated.

This concludes my presentation. Thanks for your attention, and Dr. Karen Lechter will be our next speaker.

DR. LECHTER: I will first talk in general about label comprehension studies, what they are, and how they're used. Then I'll discuss the Plan B label comprehension study. I'll finish with the agency's primary conclusions from that study.

The purpose of label comprehension studies is to test the proposed labeling with potential consumers. Questionnaires should be based on communication objectives that are the messages in the label that should be communicated, and that should be tested in the study.

The results of the studies are used to refine the labeling, which is sometimes then retested. The improved label is usually used in an actual use trial, which tests the overall use of the product. However, label comprehension studies can test issues that can't be tested in the actual use trial, such as whether people understand what the most common side effects are.

Label comprehension studies test potential consumers and also sometimes those who should not use the product. These studies are usually conducted in shopping malls. Mall participants may be supplemented with participants from other locations.

We ask sponsors to include a substantial number of low literate participants. Some studies deliberately recruit specific populations that have particular medical conditions or who use particular drugs. These participants may be recruited by telephone or by other means.

Label comprehension studies begin with a collection of initial data about participants who then usually take a literacy test. The interviewer shows the labeling to the participants and then asks questions based on the communication objectives.

The types of questions used can be yes/no, true/false, multiple choice, checklists, or open ended styles of questions. We discourage the use of yes/no and true/false questions, but if they are used, we encourage follow-up questions to determine the nature of the participant's understanding about the issue.

We encourage the use of scenario questions in which participants have to apply the labeling information to hypothetical situations, and we usually ask for a question to determine if participants can correctly decide whether the product is appropriate for them to use themselves.

The way the questions are posed can affect the responses. So we watch for biases in the construction of questions. For example, we try to eliminate leading questions and series of questions that all require the same response.

In the Plan B label comprehension study, of the 663 women interviewed, 656 were eligible to participate. They ranged in age from 12 to 50. Those who were age 18 or older who had graduated from college were not tested, nor were those under age 18, not tested for literacy.

We categorized those participants who have an eighth grade reading level or below as low literate.

The first question about the indication was asked with the package removed from site. After

that question was answered, the remaining questions were asked with various parts of the label in view. After questions about the label participants were asked about their own sexual activity and contraceptive use.

Before I present the results to you, I'd like to make some comments about scoring and issues affecting the results. In addition to presenting results of individual questions, the sponsor presented results organized by communication objective. For some objectives, all questions relating to that objective needed to be answered correctly for the objective to have been successfully communicated.

However, for other objectives half of three-fourths of the questions needed to be answered correctly. In some cases, partially correct responses were scored as acceptable or correct. For example, responses to the question about the purpose of the product, for that question credit was given to a partial response that it is for contraception even though a full response was that it is for contraception after sex.

Finally, one question about using Plan B for regular contraception was dropped from the analysis because the sponsor said it was confusing. However, another apparently confusing question on the same topic was not dropped.

There are no perfect questionnaires or methodologies. Every study has weaknesses that may affect the results and the interpretation of the results. In this study there were two primary aspects to the questioning that left gaps in our ability to interpret the results.

First, because there were no follow-up questions for some of the questions we don't know if they were answered correctly or incorrectly for the wrong reasons. Also, there were no follow-up questions for incomplete or ambiguous responses.

Another problem with the methodology is that not all participants were categorized by literacy level. Despite these shortcomings, it is likely that these weaknesses did not have a substantial effect on our ability to draw useful conclusions from the study.

The next four slides present the results

organized by communication objective. For purposes of shorthand, the tables refer to those with a reading level of eighth grade or below as low lit. and those with a higher than eighth grade reading level as high lit.

Keep in mind, however, that not everyone was tested for literacy. The total column does reflect the total number of participants who were in the study altogether.

In two places, and one of them is on this slide, I have two numbers in a box. The first number represents the fully correct response, and the second number indicates the combination of correct and acceptable responses for that item.

In the low literacy and high literacy column for that question, that represents the acceptable and correct responses for that question. For nine of the 11 communication objectives, the low literate group scored statistically significantly lower than the higher literate group. The objectives for which there were statistically significant differences are indicated with an asterisk, and as you

can see, all four of those on this slide had statistically significant differences.

It's not unusual in a label comprehension study for the low literate group to score significantly different than the higher literate group on many of the communication objectives.

This slide shows the communication objectives that score 90 percent or higher overall. These objectives are that the product is not for use by pregnant women. It doesn't prevent STDs, including AIDS and HIV. The purpose is to prevent pregnancy, and it should not be used by women allergic to its ingredients.

I want to point out that the objective about using the product to prevent pregnancy after sex had four different questions associated with it. However, only one of them had the potential to permit participants to indicate that the product is for use after sex rather than before. This was the open ended question about what the purpose of the product was.

Although 90 percent said that the product was for contraception, 45 percent mentioned that it

was for use after sex.

This slide shows the communication objectives that scored 85 to 89 percent. Eighty-nine percent understood that the side effects include nausea and vomiting.

Some responses about taking the second pill 12 hours after the first were incomplete, with 69 percent giving a totally correct response of 12 hours after the first pill and 87 percent giving acceptable or correct responses. The acceptable responses usually said 12 hours without specifying 12 hours after the first pill. Eighty-five percent understood to take the first pill within 72 hours.

This slide shows the communication objectives that scored 80 to 84 percent. Eighty-two percent understood to take the pill as soon as possible after sex, and 81 percent understood that if severe abdominal pain develops, the woman should seek immediate medical care.

There were no differences between the literacy groups for this item. As you can see, no asterisks for both of these items.

Two objectives were understood by the full sample at less than 80 percent. The low literate group also scored the lowest on these two messages. We don't know if these two issues were not well understood or whether flaws in the questionnaire prevented us from determining how well they were understood.

Understanding that Plan B should not be used if there's unexplained vaginal bleeding was at 75 percent for the full sample and 69 percent for the low literate. Sixty-seven percent of the full sample clearly understood that the product is for backup, not for regular contraception. Forty-six percent of the low literate understood this message.

For this communication objective, participants had to score correctly on three out of four questions. Scores for these questions ranged from 47 percent to 85 percent. We agree with the sponsor that one question might have been misinterpreted by participants, and we don't give a lot of weight to the results for that question.

Participants who answered these question

incorrectly would have had to answer all the other questions in this group correctly to get credit for this communication objective. In the spirit of caution, we should deal with this communication objective as if it needed improvement.

There were no effects of previous sexual experience and no difference due to experience with emergency contraceptives. However, this last finding may be due to the low number of participants with prior EC experience.

So, in summary, some concepts may be less well understood than others. However, some of the lower scores here may have been artifacts of the questionnaire design. There were lower scores for the concepts that Plan B is not for regular use. Do not use it if there's unexplained vaginal bleeding. Get medical help if there's severe abdominal pain, and take the first pill as soon as possible after sex.

Some questions were well understood, including the fact that Plan B is for contraception. It does not protect against STDs. Don't take it while you're pregnant. Don't use it if you're allergic to

the ingredients. Nausea and vomiting are side effects, and take the first pill within three days.

Results of the actual use study help assess how well the label communicates in real use situations. However, the actual use study cannot provide information about certain issues that are best tested in label comprehension studies, such as the side effects.

The label comprehension study shapes the label, but it is not the final determination of approvability.

Dr. Jin Chen will now discuss the actual use study.

DR. CHEN: Good morning. My name is Jin Chen. I'm a medical reviewer from the Division of OTC Drug Products.

I will summarize FDA's review of the Plan B actual use study, the pivotal clinical trial that the sponsor submitted with this NDA. This will be followed by a brief literature review of contraceptive behavior studies associated with emergency contraception.

First of all, I would like to briefly go over some basic principles of a typical actual use study. The actual use study intends to simulate OTC setting to assess if potential OTC consumers or users can self-diagnose the medical condition for which an OTC candidate product is indicated. To assess if potential OTC users can self-select the product, that's their understanding of the indication and warnings in a proposed OTC label, and to assess if potential OTC users can self-medicate according to label directions.

The study also evaluates the safety of the product when used under OTC-like setting.

Efficacy is rarely assessed in this kind of clinical study. The study is generally designed as multi-center, open label, single arm, uncontrolled trial.

The study population in the actual use study should represent the anticipated OTC users. Therefore, subjects are generally recruited from geographically diverse OTC-like settings with minimal exclusion criteria. The study may be reached by

inclusion of specific subgroup, such as low literacy population and a certain age category.

Subjects may have unlimited access to study product during the study. They should receive minimal intervention from health care professionals during whole study process.

Now, let's look at the sponsor's Plan B actual use study. The primary objectives of this study were to test if anticipated OTC population can correctly self-select the Plan B and it can time both doses of Plan B based on their understanding of the proposed OTC label.

The second objective of this study were assessment of adverse events, frequency of multiple use, and pregnancy rate.

As an additional observation, sponsor compared contraceptive behaviors in the study population before and after study or before and after Plan B use.

This study was conducted in five family planning clinics across five states in U.S., and five pharmacy stores in Washington State. Female subjects

of reproductive age who presented requesting emergency contraceptive only were recruited. They made that decision to participate in this study after review of the proposed OTC label. They were allowed to purchase one package of Plan B at the study site during enrollment, and they could re-enroll and purchase additional Plan B during the three-month open study period.

Subjects were followed for four weeks with two contacts, at the first week and the second week, after their enrollment. For those subjects with unknown pregnancy studies or unresolved adverse events as four-week contacts, additional follow-up work was given. Data were collected by phone interview during the follow-up contacts, and a diary card that was provided to each subject with Plan B package.

Of the 665 screened subjects, 585 were enrolled. Eighty subjects were not enrolled. Of the 585 enrolled subjects, 94 percent came from family planning clinics, the remaining six from the pharmacy stores.

The age range of the enrolled subjects was

14 to 44 years. The average age was 22 years. Eighty-seven percent of the enrolled subjects completed at least high school education. Thirty percent had ninth to 11th grade education. Forty percent of the enrolled subjects had previous experience with using emergency contraception, here EC.

Ninety-three percent of the enrolled subjects completed at least one follow-up contact. Most of them, 86 percent, have two follow-up contacts. About seven percent of subjects lost to follow-up.

Based on the follow-up information provided by 543 subjects, 540 used the Plan B during the study, which was 92 percent of the enrolled subjects.

Now, I'm going to briefly summarize each of these five results. First, about self-selection, of the 540 users, 95 percent correctly self-selected Plan B by the following reasons.

Forty percent of users had intercourse without any contraception. The others had a problem with their regular contraception methods, such as

condom use failure, missed taking oral contraception pills, and four percent of users had a problem, had accident when using withdraw methods as a contraception.

Five percent of users represented 26 subjects incorrectly self-selecting Plan B during the study. Seven subjects had labeled contraindications, such as unexplained vaginal bleeding, one already pregnancy.

There were two subjects who took Plan B before unprotected intercourse. About three percent provided nonspecific reason for using Plan B.

Timing of doses. According to the dosing instruction, in the proposed OTC label 92 percent of users took the first pill within 72 hours after intercourse. Seventy-two percent of users took the second pill at 12 hours later. Overall 68 percent of users took both pills following the label dosing regimen.

The sponsor realigned second pill timing data using different dosing definition. Ninety-three percent of users took a second pill between six to 18

hours after the first pill. If needing the first pill timing criteria the same, overall 87 percent of users took both pills according to alternate second dosing interval.

Adverse events. There were no serious adverse events and no new safety signal reported in this study. The most common adverse events were transient abdominal pain, nausea, headache, and fatigue.

Contraceptive behaviors. This table shows overall change in contraceptive behaviors of the enrolled population during the one-month study as compared to one month before study. At least one such act without any contraception decreased from 60 percent before study to 20 percent during study. User withdraw method decreased from 28 percent to ten percent. Condom use slightly increased from 79 percent to 90 percent.

Remember those behavior changes were based on one-month observation during this study.

During the one-month observation subjects tended to use more effective contraception methods.

One, point, seven percent, which was ten subjects, requested the Plan B more than once during three-month enrollment period through the re-enrollment process.

Pregnancy rate. Ten subjects, which is 1.9 percent, had a confirmed pregnancy. In addition, there were 40 subjects, which was 2.6 percent, that had unknown pregnancy studies, and at the end of the study they were lost to further contacts.

In summary, the Plan B actual use study shows that 95 percent of users correctly self-selected Plan B. Sixty-eight percent of users took the first pill within 72 hours and the second pill at 12 hours later. Eighty-seven percent of users took the first pill within 72 hours and the second pill between six to 18 hours after the first pill.

There were no serious adverse events and no new statistic loss (phonetic). Subjects tended to use more effective contraceptive methods within one month observation. There were no significant differences among demographic subgroups in self-selection, timing of doses, adverse events, and contraceptive behaviors.

However, there were some limitations in this study. The formal period was only four weeks. Subjects were allowed to purchase only one package at the enrollment, although they can come back to the study site to get another package of Plan B, but they had to go through reenrollment process.

There was no literacy testing in this study.

Finally, 94 percent of subjects were recruited from clinics. Due to those limitations, it may be difficult to extrapolate the actual use study results to the OTC setting, particularly to assess non-tour (phonetic) contraceptive behaviors in target OTC population.

To address these concerns, the sponsor submitted eight literature reports regarding contraceptive behaviors related to the advanced provision of emergency contraception. The literature enclosed five published studies, two unpublished manuscripts, and one abstract. Five studies were conducted in the United States. The remaining three studies were conducted in outside the U.S., one study

each from U.K., India and Ghana. There were no raw data submitted with these studies.

The study populations were recruited from either family planning clinics or hospital based clinics. Subjects were 15 to 45 years old who come to the clinic not for emergency contraception purpose. Sample size ranged anywhere from 160 to around 1,000 subjects.

Most of those studies were of randomized controlled design, and I have two groups, treatment and control. Treatment groups received in advance one of three courses of emergency contraception pills. Many subjects had emergency contraception pills on hand before unprotected intercourse.

In the control group, subjects were told to obtain emergency contraception pill through prescription in clinics. In one study, subjects had pharmacy access to emergency contraception as an additional control group.

All subjects in both treatment and the control group received EC education, emergency contraception education, and supervision from health

care providers.

The formal period among those studies ranged from two to 12 months.

Here's a summary of the results from those behavior studies. The 08 studies, such as with advanced emergency contraception provision, were more likely to use emergency contraception pills. In most of those studies, such as with the advanced EC provision, didn't have more frequent unprotected sex, didn't decrease condom use, didn't switch to mass effective contraception.

The behavior studies are complementary to the Plan B actual use study in some degree. For example, those studies had a longer follow-up period. The sample size in some of the studies were relatively large, and finally, the advanced EC provision is the better part in those studies.

However, there is some limitations in those behavior studies, such as all studies were conducted in clinical setting instead of simulated OTC setting. All of he subjects in those studies received EC education. Three studies were conducted in foreign

countries, which may not represent U.S. population.

Six studies provided only one course of emergency contraception pills in advance.

This completes the FDA summary of behavior study. Thank you very much.

CHAIRMAN CANTILENA: Okay. Thank you, Drs. Chen, Lechter, and Davis.

We now have time for questions for FDA presenters, and I would actually like to start with a question for Dr. Lechter.

In the review in the document, you actually talk about concepts which were not clearly understood or for which the data were inconclusive, and really a couple that jump out at me are things that really drive the primary efficacy in terms of the ability to take the first tablet as soon as possible after intercourse and the second in terms of the timing of the second dose.

And I guess overall if you do sort of the score card, I guess I have according, you know, to your information that really four of the 11 objectives in the comprehension study, you know, were not met.

And my question is: was your office involved or was the over-the-counter office involved in sort of going forward with the actual use after a study which I think if you look at other studies that, you know, we've heard about in the past for statins and the heartburn drugs, the overall success of the comprehension study was really not that good?

So my question was, you know: were you involved with shaping the label for the actual, you know, use, and if you were, I would ask, you know, why you didn't ask for a second comprehension study that was done in advance of the actual use study.

DR. LECHTER: Actually I had no involvement. There may be someone else on our team who's more appropriate to answer that question.

DR. ROSEBRAUGH: I'll take a swing at it anyway. We were not involved with the label that went into the actual use study, and it's usually the sponsor's call on when they feel like they're ready. Typically what you will see is somebody will do a label comprehension study, make changes that they think are necessary, and then they'll go into an

actual use study.

CHAIRMAN CANTILENA: Okay. Over here. Dr. Hager.

DR. HAGER: I have a couple of quick questions. One, since only 29 of 585 of the subjects in the actual use study were 14 to 16 years of age, and since those 18 years of age and younger were not tested for literacy, indicating not tested for understanding, are there any considerations about age restriction on the availability?

Number two, the comment was made that there was failure to understand the need for getting medical help for abdominal pain. The Washington State data, if you look at the pharmacy data, indicates that the pharmacist said that 85 percent of the subjects needed medical follow-up, needed medical information. Is there concern about failure to diagnose ectopic pregnancy among this population?

And finally, I have a question about effectiveness. Since you accepted an extension from 12 hours for the second dose to 12 to 18 hours, can you tell us about effectiveness with that six-hour

delay?

CHAIRMAN CANTILENA: Does someone from FDA want to handle those in order?

DR. ROSEBRAUGH: Well, in order, I think Questions 1 and 2 are things that we are awaiting panel discussion on. So I think it would be premature for us to comment.

Section 3 or Question 3 is also something that I think we are awaiting the panel to comment. I don't know.

CHAIRMAN CANTILENA: Okay. So the short answer is that you have no comment at this point.

DR. ROSEBRAUGH: Correct.

CHAIRMAN CANTILENA: Okay. Dr. Trussell and then Dr. Tinetti.

DR. TRUSSELL: I wanted to follow up on two questions that were asked before, including now a third by Dr. Hager, and it's a question, I think, to Dr. Davis.

On page 8 in Tab 5, Table 3, you have the results of two randomized clinical trials, both of which showed that a single 1.5 milligram dose, both

pills taken at once, was just as effective with no greater incidence of side effects.

We saw both from the label comprehension and from the actual use study that one of the sources of problems is people taking the pill exactly 12 hours later, which was declared to be the correct answer, and now the sponsor has even volunteered to put in a card showing the time of the first dose and the time the second dose is supposed to be taken.

We now have these data from two randomized clinical trials that show that they can be taken at once. We can eliminate all of these problems by just simply changing the instructions to take both at one time. You have ample data to support it. This change has already been made based upon the same two studies in France and in the United Kingdom.

CHAIRMAN CANTILENA: Okay. That question, I guess, was for Dr. Daniel (sic), but I guess anyone from the FDA. Would you like to comment on that?

DR. GRIEBEL: Yes. We're aware of those data as well. The regulatory process for changing the label, however, requires us reviewing those data, the

primary data, and that would be our process for doing that.

We do not have those data at this time to go through the formal review that is required to do that. So we have the prescription product before us, which had the primary data reviewed, and that's what we're working with.

DR. TRUSSELL: But the consequence is going to be unfortunately that most other medical authorities in the United States, including Planned Parenthood Federation of America, all have switched to taking both pills at once.

So there's going to be a great source of conflicting data out there to the consumer with both of these sets of instructions.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Tinetti.

DR. TINETTI: My question relates to the actual use study and which I suppose we're supposed to extrapolate from the results on the knowledge and effectiveness and appropriate use. My question is 94 percent of those people were recruited from clinics,

and do we have data on how many of them were actually instructed in the purpose, the timing, the dosing, and so is it really an accurate reflection of what's going to happen in real actual use when people aren't necessarily getting it from clinics?

DR. ROSEBRAUGH: The whole purpose of an actual use study is to try to mimic OTC environment as much as possible, and so that they were not supposed to be instructed in any use of it other than what they could get out of the labeling.

CHAIRMAN CANTILENA: Okay. Dr. Davidoff.

DR. DAVIDOFF: Yes. I had two questions. The first has to do with limitation of most of the studies, at least the published studies, and that is that an actual use, that they did not charge for the drug. The drug was supplied to the participants. As I understand it, the drug was charged for in the sponsor's actual use study.

It seemed to me that the lack of information on the effect of charging for the drug is a substantial limitation. It could work in one of two directions and possibly others. One is charging

would, of course, potentially decrease the potential for repeated use and substitution of emergency contraception pills for other more conventional methods of contraception.

On the other hand, charging obviously can and probably would decrease access to some degree. I wondered if you would comment on that particular limitation of the data that's available. That's the first question.

The second has to do with the issue of abdominal pain because it seemed to me from the labeling the significance of abdominal pain is very ambiguous. It is directed primarily at the concern about ectopic pregnancy, quite appropriately, but it seemed to me that this lack of information and the ambiguity of the message about abdominal pain could be interpreted by women as potentially a side effect of the drug, even though it's not mentioned under side effects, and I wondered if there isn't an argument to be made for spelling out in a little bit more detail why there is concern about abdominal pain.

CHAIRMAN CANTILENA: Okay. So if I can

then try to summarize, your questions for FDA are to address the issue of charging or not charging in the studies, and the other is the interpretation of the finding of abdominal pain or the message.

Curt.

DR. CHEN: Well, I can answer the first question. I guess the second question maybe give somebody else.

Actually he brought out a very, very important point to FDA. This is a big issue, either charge or not charge. For this study particularly, actually such as were reimbursed in the end of -- after second contact from my understanding, but they were told they would get reimbursed after enrollment for this one.

So somehow this confining factor here, definitely, but if you don't pay, if you don't reimburse, then you probably bring up another issue as you just mentioned. So this is very tight (phonetic), and we certainly would like to hear your suggested opinion on that.

For the second question, I guess I have to

pass to -- this is related to ectopic pregnancy, I believe, right? So probably --

DR. DAVIS: Since abdominal cramping, pelvic cramping is a normal and common side effect of the medication, there is then a fine distinction between how much cramping and pain would be then synonymous with or a potential warning signal for an ectopic pregnancy.

Our general feeling was that if severe symptoms persist for greater than 48 hours, that certainly that should be in the label for a reason to contact your health care professional, or even potentially we could label for pelvic pain on one side greater than the other. In other words, we're certainly open to a label change that would reflect the potential risk of an ectopic pregnancy.

CHAIRMAN CANTILENA: Okay. We have Dr. Crockett and then the last question from Dr. Benowitz.

DR. CROCKETT: Yes, thank you.

My question is for Dr. Chen, and it's concerning the actual use study. It struck me in reviewing the actual use study that the company did a

really good job of following the Weight Watchers model. They applied education and accountability to taking their product and saw behavioral changes that were very favorable.

And my question to you as an FDA member is: how did an actual use data get done? I want to go back to before it was done. How did it go through the FDA? And what kind of input did you as a group have concerning the design of that study that doesn't actually show actual use patterns at all?

DR. LEONARD SEGAL: Excuse me. I think I can take this question if it's all right.

I'm the medical team leader in the Division of Over-the-Counter Drug Products, Andrea Leonard Segal, and I was part of that earlier process.

And we met with the sponsor on more than one occasion, and it was clear that, see, what we try to do in actual use studies is we try to get an all comers population. If somebody wants to go into a drug store and purchase a decongestant, we would like to know that they can differentiate the product that we're interested in studying from the product that

they might actually have sought to purchase.

So consequently, we would like to have a mall setting where we would garner people from all different kinds of realms with all different kinds of purposes. However, this product deals with a very intimate issue, and the agency recognized at the time that we were discussing the protocol design that it might be very difficult for anyone to recruit this kind of a population that might be interested in this kind of an issue in a general mall setting.

So we agreed that it would be okay to use a more precise environment. This is not the first time we've done this in actual use studies. We've done this kind of thing to help sponsors target specific populations at risk when we've been concerned about perhaps somebody with heart disease who might be at risk for a particular product or somebody with kidney disease. That kind of a thought runs through our minds. So that's what we did in this particular case.

Does that address your issue?

DR. CROCKETT: Yes, partially it does. I

have less issue with the fact that it was done in a clinic setting than I do with the study structure where the patient received education and had some accountability. They knew that they were going to have to fill in a card. There were going to be contacts, and that accountability in and of itself affects behavior.

And when we're talking about taking something over the counter without that education and that behavior it seems like the sponsor's actual use study is more supporting a behind the counter or prescription setting for this drug.

DR. LEONARD SEGAL: The participants in this study were not supposed to be targeted to receive specific education. That was only the label was supposed to educate them. That's how this study differed from the behavioral studies that were used as supportive evidence for longer use where consumers or participants did receive education, both in the control groups and in the advanced provision groups. In this study education was not a specific element.

With regard to follow-up contact, all

actual use studies suffer from this weakness. We are always debating how to derive our data without influencing consumer behavior, and we try to do it in the least obtrusive manner.

But we recognize that it's a flaw. I don't think that it is possible; at least we have not figured out yet how it is possible to conduct a perfect actual use study that would not in any way influence a consumer.

What we often try to do is to not establish routine follow-up visits as much as possible. We try to allow the consumer to have as much rein as to determining when he or she will choose to follow up, but we need some means of data collection.

Does that answer the question?

CHAIRMAN CANTILENA: Okay. Thank you.

And the final question from Dr. Benowitz.

DR. BENOWITZ: My question is to Dr. Chen.

In your review of the contraceptive behavioral studies that were not done by the sponsor but published elsewhere, you talked about emergency

contraception in general, and it's my recollection, but please correct me if I'm wrong, that these included both combination estrogen/progestin, as well as progestin only products.

And it's also my impression that the side effect profile is different; that there's much more nausea and vomiting and much more aversive to use the combination products rather than progestin alone.

And do you think that that difference has any impact in terms of how people use this repetitively, in terms of contraceptive behavior?

DR. CHEN: Regarding behavior, actually I believe you referred to a literature study, right?

DR. BENOWITZ: Yes.

DR. CHEN: Okay. Yeah, some study definitely use combination products. Probably most of them, they use Yuzpe regimen.

Do you have another question?

DR. BENOWITZ: Well, my question was the toxicity of the combination product is different and more adverse than the progestin only.

DR. CHEN: Yes, in general, yes.

DR. BENOWITZ: Many women I know have taken the combined product, find it very uncomfortable and really don't want to use it again if they can ever avoid it because they get really sick.

The progestin product does not do that, and my question is does that difference in the product influence your interpretation of the contraceptive behavior and repetitive use behavior.

DR. CHEN: Yes, it could be it could impact, you know, in terms of compliance to take a pill, you know. In general, single ingredient has had less side effects from previous clinical safety trial. So that probably somehow increased compliance in terms to take both pills or one pill, whatever.

DR. BENOWITZ: So, again, a follow-up. Is there any evidence that there's a difference in behavior if you're using combined versus progestin only?

DR. CHEN: We don't have this information from those literature.

Dr. Davis, you may have something?

DR. DAVIS: Just to make a quick comment

since I did the review of the original data for Plan B and it was comparative to the Yuzpe trial from the large World Health Organization trial. There's no doubt that the safety profile, and you're referring to nausea and vomiting, was really superior for levonorgestrel only, and that, in fact, superiority claim was granted to Women's Capitol Corporation, and it is labeled such in the Plan B product.

We did not grant a superiority claim for efficacy because it wasn't statistically significant, but the data certainly strongly suggests that the levonorgestrel only is a better product for efficacy than the Yuzpe regimen.

But in comparing the behavior studies, we really -- I'm aware of the fact that many of them were Yuzpe only. One of them switched from the Yuzpe regimen to levonorgestrel only about halfway into the study, but we didn't really look at a comparison then of the two.

But it would be to me logical to conclude that the levonorgestrel only would have a better compliance profile because of the less side effects

and reuse profile, too.

CHAIRMAN CANTILENA: Okay. Thank you very much.

And we'll now move into the section of the committee meeting, the open public hearing, and Dr. Templeton-Somers will read a statement before we start this section.

DR. TEMPLETON-SOMERS: Hello. We have a very full open public hearing today. In the interest of both fairness and efficiency, we're running it by some strict rules.

To make the transitions between speakers more efficient, all speakers will be using the microphone in front of the audience. That's at the end of the table there.

Each speaker has been given their number in the order of presentations, and when the person ahead of you is speaking, we ask that you move to the nearby next speaker chair, which is in the corner by Dr. Alfano there.

Individual presenters have been allotted two minutes for their presentations. The two group

presentations have been allotted three minutes. We will be using a timer, and speakers who run over their time limit will find that the microphone is no longer working.

(Laughter.)

DR. TEMPLETON-SOMERS: We apologize for the need for the strict rules, but we wanted to give as many people as possible an opportunity to participate and to be as fair as possible.

Thank you for your cooperation.

CHAIRMAN CANTILENA: Okay. Both the Food and Drug Administration and the public are trying to have this a transparent process for information gathering and decision making. To insure transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the

sponsor, its product, and if know, its direct competitors. For example, this financial information may include the sponsor's travel lodging or expenses, you know, covering your testimony.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not stop you from speaking.

And I think we're ready to start. I will just go over one more thing. At the end of the table, you'll find a box with some lights. The lights are a code to tell you 90 seconds the light will be green. For the last 30 seconds it will turn yellow, and when your time is up at two minutes, it will change to red, and that's the point where you will no longer find the microphone is working.

Okay. We have a technical holdup here. Stand by.

Okay. I think we're ready to start. Go ahead, our first speaker.

DR. GOLD: Good morning. As an associate professor in adolescent medicine in the Department of Pediatrics in University of Pittsburgh, I'm delighted to be here today to present our research on providing emergency contraception, or EC, in advance to adolescent girls.

The results of this study will be published this February in the Journal of Pediatric and Adolescent Gynecology.

Next slide, please.

I first want to acknowledge our funding sources as well as the collaborating students who held with the project.

Next slide when you get to it.

We conducted a randomized study comparing the sexual and contraceptive behaviors of girls given education, plus one packet of advanced EC versus those who got education only. By advanced EC, I mean we gave the girls the medicine to have on hand in case they had unprotected sex.

We recruited 301 sexually active girls between the ages of 15 and 20 from an urban adolescent

clinic in Pittsburgh. At enrollment, we conducted a 15-minute interview to collect demographics and sexual and contraceptive history.

Then the girls were randomized into the advanced EC or education only group. We then conducted monthly ten-minute telephone interviews for six months.

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The two groups were well matched on relevant demographic, sexual, and contraceptive history variables. We found no difference by groups in rates of unprotected sex or in the use of hormonal contraception at the one and six-month follow-up interviews.

There was also no difference by group in condom use at the one month follow-up.

Next slide, please.

However, at the six-month follow-up, more girls in the advanced EC group used condoms in the past month compared to those in the education only group. The advanced EC group used EC nearly two times more than the education only group at the one-month

follow-up.

More importantly, the advanced EC group started their EC course sooner after unprotected sex compared to the education only group. EC is 50 percent more effective when taken within 12 hours of unprotected sex.

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These findings imply that having EC easily available does not cause adolescents to have more unprotected sex or to stop using hormonal contraception or condoms. It does help adolescents use EC sooner.

Thank you.

CHAIRMAN CANTILENA: Just made it.

(Laughter.)

CHAIRMAN CANTILENA: Okay. Next speaker, please.

(Applause.)

DR. CULLINS: Good morning. I'm Vanessa Cullins, Vice President for Planned Parenthood Federation of America.

I have no financial relationships with the

sponsor.

Planned Parenthood Federation of America wholeheartedly supports Plan B emergency contraception becoming over the counter. As you have heard, Plan B emergency contraception is ripe for over-the-counter availability.

Planned Parenthood Federation of America has followed the extensive body of published literature about emergency contraception pills which consistently shows that emergency contraception is safe, effective, and is used responsibly. Based upon this evidence, the federation has striven to make emergency contraception easily accessible through such programs as Dial EC, through which a prescription is phoned into a pharmacy; Emergency Contraception Online; advanced provision of emergency contraception pills or prescription; and emergency contraception to go through which a walk-in visit results in express availability of emergency contraception.

Since 2000, over two million emergency contraception kits have been purchased from Planned Parenthood affiliates. Based upon affiliate

experiences, we confirmed that emergency contraception is used as intended, and women do not use emergency contraception as regular contraception.

Within the federation, which consists of over 850 clinical sites, there have been no reports of serious adverse events attributable to emergency contraception.

Over-the-counter availability insures timely access to a safe medication which works best the sooner it is taken. Continued prescription or over-the-counter status encumbers timely access to emergency contraception.

Even in Washington State where collaborative pharmacy agreements create an environment that's similar to behind-the-counter access, consumer need is not satisfied. All Washington State family planning affiliates have had a marked increase in the amount of emergency contraception that has been purchased and used by women.

Over-the-counter status --

CHAIRMAN CANTILENA: I'm sorry, ma'am.

Your time is up.

DR. CULLINS: -- important and timely.

(Laughter.)

CHAIRMAN CANTILENA: Thank you, ma'am.

The next speaker, pease.

DR. STUART: Good morning. My name is Dr. Gretchen Stuart. I'm an assistant professor at the University of Texas Southwestern Medical Center in Dallas, and I'm a practicing OB-GYN, and I'm testifying today on behalf of the National Family Planning and Reproductive Health Association, known as HFPRHA.

I have no financial or other conflicts of interest with Plan B or any other drug companies to disclose.

NFPRHA represents a network of 4,600 clinics which provide family planning services to low income women across the country and are supported with federal funds, such as Title X.

Title X clinics have been on the forefront of efforts to provide emergency contraception in a timely fashion. We salute Barr for making a public

commitment to continue selling Plan B at a reduced price to Title X providers.

However, based on first-hand experience, this is not enough. For many uninsured women and teens, the barriers to EC access remain insurmountable. Many have little experience with the medical system and may be too intimidated to make a call to a health care provider to ask for a prescription.

Many clinics are closed on nights and weekends, and many pharmacies fail to stock EC as a prescription product.

For these reasons I couldn't be more supportive of removing any barriers to accessing Plan B for teens. Currently 80 percent of all teen pregnancies are unintended. This statistic necessitates action based on the reality of teens' lives rather than our collective wish that teens postpone sexual activity.

Like it or not, nearly half of all teens are sexually active by the time they graduate high school, and like all women, teens are not always

effective contraceptive users and can experience failure.

The economic and social consequences of unintended teens specifically are devastating. Less than one third ever finish high school and leaving many unprepared for the job market and likely to raise their children in poverty. Fifty-two percent of all mothers on welfare had their first child as a teenager.

Given the clarity of the science and the enormous potential to advance the important public health goals of reducing unintended pregnancy and abortion, I strongly recommend that FDA allow Plan B to be placed over the counter on pharmacy shelves and not behind the counter restricted.

Thank you.

CHAIRMAN CANTILENA: Thank you, Dr. Stuart.

Next speaker, please.

MR. MARSHALL: My name is Robert Marshall. I'm a state legislator from Virginia.

As I look around the room today, one name

that should be on this NDA is Hugh Hefner. Playboys, adolescent adult males are going to be the primary beneficiaries of this. In fact, I will suggest to you they may be the major purchasers of this, who in turn will sell it to high school kids that we're going to have to deal with with appropriations from the State of Virginia.

Cokie Roberts says, "I always love the demographic figure on abortion. The most pro choice group in the country, young men between the ages of 18 and 25, the most responsible group well known for taking, you know, responsibility for their actions."

Why isn't NDA even considered here? The U.S. Defense Department authorized this for one month, then pulled it off its formulary. At the University of Virginia, these pills are passed out up to 120 hours after intercourse. Physicians there at the medical school are refusing to pass this out.

You all said it was safe. You said it's effective. Perhaps this causes abortion and perhaps of them have a conscience about this and don't want to be forced into this like they will be.

This drug was never proven safe in the first place. Industry watchdogs have, in fact, become industry lapdogs. The FDA did not rely upon any independent test conducted for safety or efficacy. You cited 21 studies, 19 of which dealt with efficacy. One maybe dealt with safety dealing with blood clotting. One from Kaiser Permanente showed that almost 50 percent of women had moral questions about what was going on.

Additionally, I found out the incidence of abortion will not be reduced. I looked at your Web site this morning. Interestingly, the definition of pregnancy has been changed even by the Bush administration from fertilization to implantation, and I've got the proof back here. This was from May 13th to yesterday.

The definitions of abortion and pregnancy were defined and acknowledged by Dr. Abraham Stone, who said, "Measures that prevent implantation are measures that cause abortion." He's from Planned Parenthood. I loved quoting my opponents.

You all are doing a disservice, and you

will disrespect the rights of women to be informed as patients to call this --

CHAIRMAN CANTILENA: I'm sorry. Your time is up. Thanks, Mr. Marshall.

The next speaker please.

MS. LASER: My name is Rachel Laser, and I'm senior counsel with the National Women's Law Center.

I have no financial or other conflicts of interest with Plan B to disclose.

The mission of the National Women's Law Center is to reduce barriers for all women with special attention to the needs of low income women. Making Plan B an over-the-counter drug removes barriers to access of this critical contraceptive drug for women and, in particular, low income women.

Women do not use EC in great part because they lack access to it. Barriers to access include gaps in knowledge, obstacles to obtaining a prescription, time constraints and costs, factors that are all exaggerated for low income women.

In order to obtain EC as a prescription

drug, a woman must first know that it is an option. Low income women are more likely not to have heard about EC. Positioning EC over the country where it is easily accessible helps to educate all women about its availability.

Next, the woman wanting EC must visit a physician to get the prescription. Nearly one in five women, however, and nearly one-half of uninsured women do not have a regular health provider. These women are hard pressed to obtain an appointment with a physician on such short notice.

A woman must also be able to pay for the visit, plus transportation both to the doctor and then the pharmacy. Secondary costs might include missed work and babysitting. Making EC available over the counter would eliminate many of these hurdles.

Finally, we note that the cost of EC over the counter relative to the sometimes lower cost of EC as a covered prescription drug could impede access for some low income women. For women who have insurance coverage though EC might be off formulary and cost at least as much as it would over the country, and many

of the low income women do not have prescription coverage for this product. Nearly one in five women lack health insurance, the majority of whom are low income women.

And although all state Medicaid programs must cover family planning services, almost half of the states do not cover emergency contraception and Medicaid programs.

Finally, public funding could help minimize the cost of EC over the counter.

In summary, although some low income women may benefit from prescription coverage of --

CHAIRMAN CANTILENA: I'm sorry. Your time is up. Thank you, Ms. Laser.

The next speaker, please.

DR. STEWART: Good morning. My name is Felicia Stewart. I chair the board of directors for the Association of Reproductive Health Professionals, an organization of 12,000 reproductive health researchers, educators, and clinicians in the United States and internationally.

I also am an adjunct professor in OB-GYN

and reproductive sciences at U.C.-San Francisco.

On behalf of ARHP, as well as the 3,000 members of the National Nurse Practitioners in Women's Health and the 10,000 members of the American Medical Women's Association, I'm pleased to have an opportunity today to speak in support of switching Plan B to over-the-counter status.

ARHP manages the first national emergency contraception hotline and Web site established in 1996 to provide women with information about emergency contraception and referrals to providers. To date our Web site has received over two million visits and approximately 500,000 phone calls.

ARHP also received calls and E-mails from women seeking help. The preponderance of these, and I have to deal with my fair share of them, is not because of problems they have using the medication, but because they have problems finding access to the medication.

Better access is needed. Seeing a provider is not necessary and certainly can be a barrier since this option can be used safely and

effectively without prescriber intervention.

We also note that there are some ethical issues involved. It would be unethical to withhold from women a safe, effective treatment that affords a second chance and also unethical to reinforce the idea which woman naturally would assume on the basis of FDA restriction, that there would be some scientific evidence that unrestricted use would be unsafe or dangerous for their health.

Finally, there is unprecedented support for this. ARHP, along with 70 organizations --

CHAIRMAN CANTILENA: I'm sorry. Your time is up, Dr. Stewart.

The next speaker, please.

MS. WRIGHT: I'm Wendy Wright with Concerned Women for America, which is the nation's largest public policy women's organization. We have no financial ties to the sponsor, to the product, or to its competitors, and we're very disturbed by Plan B's promoters' emphasis on access, but not on women's safety.

There have been no studies done on the

long-term effects of women after taking Plan B. There have been no studies on the effects of multiple use. In fact, Plan B promoters liberally encourage multiple use. On Plan B's Web site in the Q&A section, it asks how often can Plan B be provided. The answer is Plan B can be provided as frequently as needed.

Additionally, there have been tests done in the pediatric population which is now required by federal law. The Pediatric Equity Act of 2003, just signed into law on December 3rd, requires this.

Consumers are more influenced by ads than they would be by labeling, and the ads that have been put out by Women's Capitol Corporation for Plan B have actually been found in violation of federal law. I will quote from the FDA's letter to Women's Capitol Corporation.

The FDA has concluded that Women's Capitol Corporation's ads are false, lacking in fair balance or otherwise misleading, in violation of the Federal Food, Drug, and Cosmetic Act. Specifically, the direct to consumer radio and print ads overstate efficacy, fail to convey important limitations on use,

and minimize important information about risks associated with the use of Plan B tablets emergency contraception.

As a result, the ads raise significant public health and safety concerns. We have provided a full testimony that refutes many of the claims made today by Plan B's promoters that I'll not be able to include in this short testimony.

We've also raised concerns not addressed by the promoters. I would encourage you to please read our full testimony.

Thank you.

CHAIRMAN CANTILENA: Thank you.

The next speaker, please.

MS. FREEMAN: Hello. My name is Linda Freeman. I am the co-chair of the NOW New York State Reproductive Rights Task Force. I am speaking to you today not only as an activist, nor as someone who has used the morning after pill, but most importantly I'm speaking to you today as a woman, a woman who has found access to the morning after pill to be a challenge.

I had just moved from Ohio to New York City and was in my first year of graduate school. My boyfriend had come up for the weekend to visit and our Plan A method of birth control failed and I found myself in need of the morning after pill. What I found may or may not surprise you. It was sure a surprise to me.

Many of the health clinics I phoned wanted between 50 to $150 for a doctor's visit and a prescript for EC. As a graduate student, which all of you were at one time or another, you know that a student's budget is extremely limited. I cannot afford such exorbitant costs.

I continued to phone health facilities throughout the New York City area, hoping that I would find some place that was much more reasonable. Unfortunately I did not. what I did find, however, was the student health center at the school that I was enrolled in. They had the pills in stock, and I was urged to come into the center immediately.

I was lucky but many women are not so lucky. Now that I am out of school I have no longer

the peace of mind knowing that the morning after pill is available to me when I need it as long as it's Monday through Friday from nine to five, the hours in which the clinic is open. The cost is now a bit more for me than as a student. Unfortunately my health insurance does not cover birth control pills. It does, however, cover Viagra.

In the past, on Friday, I had an appointment with my OB-GYN, who refused to write me a prescription for the morning after pill, stating that I needed to contact him first to make sure that the need for the pills was warranted, as if I wouldn't know when I needed to take them.

Please keep in mind as you are making your recommendations today that we women are aware of when we need to take the morning after pill. Please do not insult our intelligence nor belittle us. We as women are capable of following directions.

Most importantly, we as women should and must be allowed to make reproductive decisions for ourselves without interference from others, without judgment from others, and without the need for someone

else' approval.

Thank you for your time.

(Applause.)

CHAIRMAN CANTILENA: Thank you.

Next speaker please.

MS. DENNER: I'm Carole Denner. I'm a registered nurse with 35 years' experience, and I'm a volunteer with Concerned Women for America.

Over-the-counter labeling conveys the impression a drug has been proven safe as user's labels without any hidden health risks. Neither the 21 studies cited by the FDA in the 1997 invitation for new drug applications, the 39 studies cited by the Women's Capitol Corporation in this over-the-counter application, nor the studies referenced by Dr. Daniel Davis this morning address the long-term potential health consequences to America's women and girls.

What is the maximum safe dose of levonorgestrel monthly or yearly? None of the clinical trials cited were designed to determine any long-term risks based on expected variables for adolescents, women over age 35, concomitant medical

conditions.

It was mentioned this morning under need that 43 percent of U.S. pregnancies will experience problems. The greatest percentage of these occur in immigrant or in educated populations, women who choose not to avail themselves or who delay the available prenatal care that is available in the United States. None of the studies cited follow the participants beyond the immediate time frame of levonorgestrel usage. Are there long-term risks?

Taking only one and a half times the recommended daily dose of Tylenol for more than ten days can result in hepatotoxicity, but this wasn't even determined until Tylenol had been on the market for years.

What is the risk to America's women and girls?

The American Medical Association and the American College of Obstetricians and Gynecologists both recommend Plan B go over the counter. Yet they continue to recommend that low doses of the same drug given as a normal birth control pill be given only by

prescription. That's how logical and inconsistent.

For the safety of American women and girls, I and the over half a million members of the Concerned Women for America of Virginia, the nation's largest public policy women's organization, ask and recommend that high dose hormone therapy after unprotected sex be available only by prescription by those capable of evaluating women for their health risks.

Thank you.

CHAIRMAN CANTILENA: Thank you. Time's up.

Next speaker, please.

MS. MAHONEY: Hi. My name is Erin Mahoney. I am the Co-chair of the National Organization for Women, New York State Reproductive Rights Task Force.

There are many reasons why the morning after pill should be over the counter, but in these two minutes I have with you, I want to talk about my experience with the morning after pill and why I needed over the counter.

When I needed the morning after pill, I was in Detroit, Michigan for the first time. I had just helped my boyfriend move and we didn't know a sole. We used condoms as our birth control method, but this time I needed the morning after pill. I was luckier than other women in this place. I had gone to a feminist gynecologist that year, and she had insisted that I take a prescription for the morning after pill with me in case I ever needed it.

However, that pill was not cheap. That doctor's visit cost me $150 because my insurance didn't cover annual gynecological exams. It does cover Viagra.

I had the prescription for the morning after pill filled that day and kept it in my medicine bag until that night when I needed it. If I had not had the morning after pill with me, I would not have had the first clue where to start looking for a doctor's office in Detroit, let alone one open on a Saturday night when I needed it.

I read the instructions. I followed them exactly, took the first pill with food and then the

second 12 hours later. I didn't get sick or throw up. I was just relieved I wasn't going to get pregnant.

But what really bothers me about this whole process is that if I happen to go to a good doctor that is willing to write me a prescription just in case I need it, I'm lucky. If I go to a doctor who refuses to prescribe it in advance, I'm out of luck.

I shouldn't have to rely on luck to control my life. I shouldn't have to rely on a doctor for a drug that is safe and effective within the first 24 hours after sex.

We have a lot of experts in the room today, but I have taken the morning after pill, and I know what could have happened if I hadn't had it on hand, and I know what could happen to me if it isn't over the counter. I think that makes me an expert.

Because many of us who have experienced the morning after pill have so little time to talk here, we're going to speak outside at the lunch break for the press about our experience taking the morning after pill.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Our next speaker, please.

MS. HARRISON: Good morning. My name is Teresa Harrison of Ibis Reproductive Health, a nonprofit organization that aims to improve women's health choices on autonomy. I'm also on the board of directors of Our Bodies Ourselves, a women's health advocacy group.

Neither organization receives funding from pharmaceutical companies.

Both Ibis and Our Bodies Ourselves support the switch of Plan B to the over the counter. In particular, we support the switch because what we have learned about women's efforts to obtain emergency contraception.

Ibis research shows that women cannot get emergency contraception when they need it. America's ERs turn women away in their hour of need. Recently we surveyed over 1,200 hospital emergency rooms across the country. Less than half would provide emergency contraception to women, even those who have been raped.

Just 16 percent would provide it to any woman who needed it, and an additional 18 percent would only provide it to women of sexual assault.

Our research also found that ERs staff are frequently judgmental or even hostile towards callers. Some ER staff do not value women with contraceptive emergencies.

If Plan B were available over the counter, women without health insurance, women without private doctors, and women who need it on weekends could get EC directly, discretely, and with dignity. They could also avoid an unpleasant and expensive, time consuming visit to the ER.

Please allow Plan B to go over the counter.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

Next speaker please.

DR. KLAUS: I'm Hanna Klaus. I'm an obstetrician-gynecologist with extensive experience in natural family planning and teen sexuality education.

I have no financial relationship with Plan

B.

I object to changing the status of Plan B for the following reasons, which are documented in detail in my testimony. There's no time for documentation here.

Progestin slows tubal motility. Both U.K. and New Zealand have warned doctors when they had a 5.9 percent rate of unintended pregnancies which were ectopic. To make a drug with that potential for an increase in ectopic pregnancy available without medical supervision is the height of medical irresponsibility.

When Plan B was the sole contraceptive of women with infrequent coitus, their unplanned pregnancy rate was 6.8 percent with a 33 percent dropout rate due to side effects within six months. People take the course of least resistance to interact to take the drug more than once per cycle, irrespective of warnings, and will likely turn away from it when they experience side effects leaving them even more vulnerable to pregnancy and STD.

The chlamydia and gonorrhea rates have

risen nearly 20 percent in this country in the last four years, concomitant to the high profile advertising of the morning after pill which, intended or not, promote the notion that taking Plan B will make up for the lack of sexual responsibility.

Women also have a right to know that Plan B, if taken after conception, prevents implantation. If they have ethical objection to aborting an embryo at any stage, they have a right to the right information.

And finally, conception can only occur in six days in the cycle, making the pills unnecessary for at least 24 days out of each cycle, and that may be fraudulent advertising.

I suggest you teach people their fertility cycle so that they'll know when to say yes and when to say no.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Next speaker, please.

MS. MOORE: Hello. My name is Kirsten Moore, and I'm President of the Reproductive Health

Technologies Project, a nonprofit advocacy organization based here in Washington, D.C.

We do not have a financial interest in this product. We do not accept any money from pharmaceutical companies of any kind.

We've been working on the issue of emergency contraception for ten years. We have greatly enjoyed our work in this field trying to raise awareness, reduce barriers to access. We've been involved in dozens of initiatives to promote advanced provision, pharmacy access, public education campaigns, et cetera. These have all been fun, but they've cost a lot of money. They've taken a lot of money. They've taken a lot of time. It takes a great deal to get buy-in from the professional medical community, and our take-away message is that medical practice is slow to change, and that it is time to put the decision about emergency contraception, when and where to use it, in the hands of women.

There is no medical or public health rationale which justifies preserving a prescription access or otherwise restricting access to this

product.

Though we are not service providers, we do have first-hand knowledge of the need for better access to EC. Our HTP was the original home of the hotline, and all too often has been on the receiving end of panicked phone calls from women who were desperate to find EC, but could not find a provider, did not wish to see their own provider, or were refused EC by a provider.

We know the prospect of an OTC switch prompts questions about the consequences of nonprescription access and the fear of misuse, overuse, or general irresponsibility. We understand these concerns and fully support effort to insure informed responsible use of EC among women of all ages.

However, concerns about consequences of too much access cannot overshadow the real consequences of the current situation: difficult access, limited access, or no access to health care in EC specifically lead to distress, unintended pregnancies, and abortions. It does not have to be

this way. Every woman including young women deserve a second chance to prevent an unintended pregnancy.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Next speaker, please.

DR. JORDAN: My name is Dr. Beth Jordan. I'm the Medical Director of the Feminist Majority Foundation, a leading feminist think tank, grassroots organization, and publisher of Ms. Magazine.

We have no financial incentive or relationship with Barr.

With the largest pro choice student activist in the U.S., the Feminist Majority is committed to working with students and providers to maximize access to emergency contraception on the nation's campuses. Other speakers are to discuss EC safety and efficacy in reducing unintended pregnancy and the abortion rate. I can unique inform you of the situation on campuses by discussing the results of a recent social science study conducted by the Feminist Majority Foundation documenting the lack of availability and inaccessibility of emergency

contraception.

College age women are at particular risk for engaging in unprotected intercourse, experience contraceptive failure, and being sexually assaulted. To the maximally effective, EC must be taken within 24 hours. Barriers to timely access place unnecessary and unacceptable burdens upon students.

In 2002, the Feminist Majority Foundation conducted a comprehensive nationwide random sample survey of EC access on campus health clinics. The survey found that only 61 percent provide EC or prescriptions for EC, and only 16 percent have weekend hours.

Anti-reproductive rights politics is an obstacle threatening access to EC on campuses. Anti-abortion legislators and activists who wilfully or naively can cite contraception with abortion increasingly infringe upon a woman's right to choose even contraception.

Leading physicians of the 2002 American College Health Association Conference reported to me that through intimidation, protests from anti-

reproductive rights legislators, office holders, and activists discourage student health clinics from offering or advertising EC. Our students deserve better.

ED access must not be dependent on right wing politics, restrictive clinic hours or the individual provider or the clinic provider. Empowering young women to be responsible in preventing unintended pregnancy requires over-the-counter access to emergency contraception 24 hours a day seven days a week.

In 2002, the Feminist Majority Foundation launched a petition gathering support for over-the-counter access to EC. I present more than 30,000 petitions to you as your token of support on behalf of legions of Americans supporting this public health measure.

The scientific evidence and public health imperative is strong and undeniable. Access delayed --

CHAIRMAN CANTILENA: Our next speaker please.

DR. CARROLL: My name is Robert Carroll. I'm a retired physician. I'm here as an individual, not representing any group or organization, and I have no financial involvement.

My interest in the question of permitting over-the-counter sales of the morning after pill stems from my concerning regarding the epidemic of sexually transmitted disease, especially among young people.

I practiced medicine as a general internist from 1949 to 1995. The increase in STDs in the last several years of my practice was startling and disturbing. For the past eight years I have been presenting elective classes on STDs to students at the local senior high school.

As everybody knows, our society has undergone a sexual revolution in the last 30 or 40 years. Our young people have been encouraged to engage in sexual activity with the understanding that it was safe and morally acceptable as long as contraceptives were used.

They were not and are not now being adequately informed of the significant danger of

acquiring STDs with or without the use of contraceptives. There are more than 15 million new cases of STDs every year in this country. Not all the news is bad. For the past ten years there has been a slow, but steady increase in sexual abstinence. This trend has been accompanied by a similar slow but stead decrease in abortions and teen pregnancies.

It is self-evident that over-the-counter availability of the morning after pill will lead to increased promiscuity and its attendant physical and psychological damage.

Thank you.

CHAIRMAN CANTILENA: Thank you.

The next speaker, please.

DR. ENGLE: Thank you for the opportunity to present the views of the American Pharmacists Association.

I'm Jan Engle, Associate Dean for Academic Affairs and clinical professor of pharmacy practice at the University of Illinois at Chicago and the immediate past president of APHA.

Decisions to classify products as either

prescription or nonprescription are best made by the FDA incorporating a review of safety and effectiveness utilizing clinical research information.

Part of the review must include examining the risks and benefits associated with increasing access to the product. Specifically, the FDA should evaluate how this product has been used in the prescription only environment to assess prescribing patterns and patient use patterns that may support expanded access of the product to an OTC basis.

The provision of the product by pharmacists under the purview of collaborative practice agreements, agreements between pharmacists and physicians detailing the conditions under which a pharmacist will initiate or modify a patient's drug therapy may support the expanded availability of a product. EC is a therapy commonly prescribed under these agreements.

Pharmacists in more than 37 states have the authority to initiate or modify therapy under collaborative practice agreements with physicians and other prescribers. In the case of levonorgestrel,

five states explicitly allow pharmacists to prescribe and/or dispense emergency contraception directly to patients under collaborative practice agreements.

A number of other states allow pharmacists to provide the therapy under collaborative practice agreements as well. Washington State was the first state to allow pharmacists to provide EC in a two-year pilot. By the end of the pilot nearly 12,000 patients consulted pharmacists for EC, 40 percent of which were during weekends and evenings or holidays.

It's important to note of the 12,000 interactions, many times pharmacists did not dispense the drug because it was not appropriate. Sixty percent of pharmacists referred at least one patient for further care; 75 percent referred patients because of concerns of eligibility; 50 percent referred for contraceptive services; and seven percent for rape counseling.

Clearly, pharmacist provision of EC under collaborative agreements significantly improve --

CHAIRMAN CANTILENA: Thank you.

Next speaker please.

MS. FLOWERS: My name is Hillary Flowers. I am 23 years old, and I recently moved to New York City from Madison, Wisconsin. I am fully employed, and I have no health care benefits.

When I needed the morning after pill, I was a sophomore in college. I called tons of doctors, but they did not want to see strangers who did not have an appointment. I finally found a female doctor who would see me.

She explained to me that the morning after pill was basically a higher dose of the regular birth control pills. She gave me a pack of regular pills and told me how many to take. I had no side effects.

The cost of my doctor's bill was between 150 to $200.

A few years later, I was in a serious relationship and the condom broke. In this circumstance I was contemplating whether or not to go on birth control pill. So I had birth control pills at my house.

I knew from my previous experience from talking to my doctor that the morning after pill was

a higher dose of birth control pill. So I took the same amount of birth control pills as I had taken before, and I recently learned that the number of pills changes depending upon the brand of birth control pills you are taking. The brand of pills I had at the time was probably not the same as I had taken, but I couldn't afford to pay $200 for a doctor's visit, nor did I want to call 20 doctors who did not want to see strangers.

I risked my health in order to take the morning after pill which was so hard to get. I'm a very healthy woman. I have no health insurance, and I am paying student loans. What am I supposed to do if a condom breaks? Not pay rent so I can pay a doctor to get the morning after pill? Take a bunch of birth control pills that I have on hand or that a friend has that I can try to borrow and take 12 hours after?

I shouldn't have to risk my health to prevent pregnancy. I must have the right to control my body and my life with directions in order to know that I'm taking the right kind of pill.

CHAIRMAN CANTILENA: I'm sorry, ma'am. Your time is up.

Next speaker, please.

MS. MANGAN: My name is Kelly Mangan. I'm the Vice President of the University of Florida Chapter of the National Organization for Women.

Women should not be told when or under what circumstances we can control our bodies. Yet here I stand ironically before a panel many of whom are men having to ask for the right to control my body and direct my life.

I have used the morning after pill twice after condoms came off inside me while I was having sex. I didn't get pregnant, and I also didn't have any of these overhyped side effects I keep hearing health professionals talk about.

I got the morning after pill from my campus infirmary to have if I ever needed it, but the nurse who prescribed it asked prying questions about my relationship with my partner and how long I had known him. She also discouraged me from taking the morning after pill again because of possible side

effects, while at the same time encouraged me to go back on birth control pills which could have far more serious side effects than the morning after pill.

If the morning after pill was available over the counter, I wouldn't have to spend time and money making doctor's appointments when I needed it. I also wouldn't have to justify myself to nurses and doctors because they disapprove of my sexual relationships, which are none of their business anyway.

If I could really control my fertility, meaning 24 hours a day and without having to bed a doctor or a pharmacist for permission, then I would have more time, more money, and more personal freedom. Basically I would have more control over my life.

CHAIRMAN CANTILENA: Thank you.

Next speaker please.

DR. BRUCHALSKI: My name is Dr. John Bruchalski. I'm a practicing OB-GYN in Fairfax, Virginia and here with the Catholic Medical Association.

The points I want to make today refer to

teenagers and Plan B. Point number one, not all women have regular cycles, especially teens. Forty-three percent of girls have irregular periods the first year after menarche. For as long as five years one-fifth of adolescent girls have irregular menses.

Point number two, it's these same women with irregular cycles who are sexually active, suffering from pregnancies and sexually transmitted diseases. We all know that two-thirds of twelfth grade women have had sexual intercourse. We also know that three to four million of the new STD cases this year will be teens.

Most teens rely on a single contraceptive to prevent pregnancy and infections when they're using anything at all. The reduced contraceptive efficacy relates to improper use and frequent discontinuation of contraception.

Conversation and counseling can help prevent this. Therefore, without medical advice from a health professional, the use of Plan B by teens will be disastrous.

Current thought also says that a physical

exam is unnecessary before treatment. We are educating our patients about their options presently. Why put this potent medication over the counter and bypass an opportunity for counseling, especially in this affected subgroup, teen women?

I know of no study specifically looking at teens and Plan B.

We are sincerely passing up an opportunity to engage our teen patients about the hazards of sexual intercourse. You've heard these stories from these presenters prior to me. It is in this conversation and counseling that they will become more open and honest with their medical providers.

Conversations lead to trust. Trust leads to following advice. Over-the-counter status decreases conversations. Over-the-counter status for Plan B is bad medicine.

CHAIRMAN CANTILENA: Our next speaker, please.

DR. KAHLENBORN: Chris Kahlenborn, Altoona, Pennsylvania.

No financial interests.

I'd like to make four points against Plan B. First, there have been no trials on the long-term effects of Plan B on children who will be conceived if Plan B fails to prevent or abort a pregnancy. Obviously children will be conceived and brought to term in women who take Plan B. There has never been a single study going out ten, 15 years on what will happen to those children, and many of us physicians and internists know well what happened with dioethylstilbesterol when it was given to women and resulted in an increased risk of vaginal cancer in their daughters

Secondly, the claim that emergency contraception has a 75 percent efficacy rate could be artificially inflated since it is based on studies whose control groups were not properly matched against the case groups. Usually older control groups or control groups that had lower rates of infertility are not properly matched. That would overinflate that statistic.

Third, women could theoretically begin using Plan B as a type of birth control. An

experience from Jamaica which made emergency contraception over the counter this past May may serve to remind us of this possibility. Quote, pharmacists from across the land as we have reported are ringing alarm bells. Some people are using it as sweets. People are using it more than twice a month. Some are using it up to five times a month.

And lastly, the evidence clearly shows that Plan B works by causing an early abortion, a post fertilization effect.

A leading professor wrote to me and said -- a leading advocate of emergency contraception -- "I think women should be told how emergency contraception works, including it might work by inhibiting the implantation" --

CHAIRMAN CANTILENA: Sorry, sir. You're out of time.

Next speaker, please.

DR. HUSSAR: I'm Daniel Hussar. I'm on the faculty at the Philadelphia College of Pharmacy, but speaking as an individual. I teach the nonprescription drug therapy course.

I do not have any financial or other working relationships with any of these companies to disclose.

I urge the members of the committee to recommend against unrestricted OTC availability of Plan B and to recommend OTC availability of this product only following a woman's consultation with a health professional as the pertinent expertise regarding its use.

And we have heard about the Washington and California models.

I'd identify the following reasons in support of these recommendations. First of all, regarding the mechanism of action, the package insert for Plan B notes that it may inhibit implantation, an action that is considered by some to be an abortifacient action. To my knowledge, there are no definitive data to identify the approximate percentage of women who may experience inhibition of implantation.

Secondly, safety. Some of the women who might consider the use of the Plan B may be pregnant

but do not yet realize it. A question then exists regarding the safety of the product for the developing fetus. To my knowledge, there are not sufficient data to demonstrate safety for a fetus. Plan B is contraindicated during pregnancy.

In reviewing the package insert for Plan B, I was very surprised to observe that unlike the vast majority of other products, there is no pregnancy category identified, and I would urge the committee to ask why that is the case or not the case.

Certain other progestins, as well as the combination oral contraceptives, are classified in pregnancy Category X, signifying the highest level of risk for a fetus. It's reasonable to think that Plan B should be classified in pregnancy Category X also.

To my knowledge, no drug that is classified in pregnancy Category X is available without a prescription.

Third, other implications, as others have mentioned. I have concerns about the extent of the risk of sexually transmitted infections. I think the availability of Plan B without restrictions would

increase or would reduce safe sex precautions which could lead to the increase in consequences, such as STDs.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Next speaker, please.

MS. BOONSTRA: On behalf of the Alan Guttmacher Institute, I thank you for this opportunity to comment on the new drug application proposing over-the-counter use of Plan B, the FDA approved emergency contraceptive.

AGI is an independent, not-for-profit organization focusing on reproductive health research, policy analysis, and public education in the United States and internationally. The institute does not have any financial relationship with Plan B, the sponsor, or its direct competitors.

Moreover, Sharon Camp, founder and former President of WCC and now President and CEO of AGI, has no financial interest in WCC.

Timely access to emergency contraception is one of the most promising avenues for lowering

unintended pregnancy and reducing the need for abortion in the United States. Most U.S. women at risk of unintended pregnancy over nine and ten are using contraceptives. But some have difficulty using contraception correctly or consistently, and contraceptive methods do fail.

Approximately half of unintended pregnancies in the United States occur among couples who are using contraceptives in the month they become pregnant. Data indicate that emergency contraceptive use has already played a significant role in reducing U.S. unintended pregnancy and abortion rates.

Even with limited access to and awareness of the method, recent AGI research finds that emergency contraception averted 100,000 unintended pregnancies in the year 2000, including an estimated 51,000 abortions.

We ask the committee to give full and fair consideration to the question of OTC status. The panel should make a science based recommendation, treating the pending application as it would any other proposed switch from prescription to OTC status.

This application should not be held to a different standard simply because the product involved is a contraceptive method.

We thank the committee and would be happy to respond to any questions it may have.

CHAIRMAN CANTILENA: Thank you.

Next speaker, please.

DR. COLLITON: My name is Dr. William Colliton. I'm a retired OB-GYN professor from the George Washington University Medical Center. I understand that you have copies of my statement, which time prohibits getting into.

I do want to draw your attention to the appendices behind the statement. The first one is a page containing two graphs that show the incidence of divorce and the incidence of gonorrhea encountered over time, the time frame beginning in 1920 and ending in 1980. You can see that there was a blip in both graphs during World War II, very, very understandable when young people are torn from their families and from their loved ones and get into extramarital intercourse and the love bug jumps up and also the

rate of divorce jumps up.

Then you see that these curves beginning in 1960 take a dramatic turn up to the upper right-hand corner of the graph going out of sight. This is because in 1960 the birth control pill and the IUD were marketed and being efficacious contraceptives and abortive agents. They gave rise to the ability to have a sexual revolution.

The second graph that I wanted to draw your attention to is a demonstration of the total ineffectiveness of the approach to eliminating teenage pregnancy under Title X. The data begins in 1971 and ends in 1999.

You should understand that during that time frame 4,085,000,000 of your tax dollars were expended in an attempt to eliminate the problem of teenage pregnancy with no effect whatsoever, except to worsen the problem.

The problem got so bad that the Alan Guttmacher Institute and the federal government stopped putting the data out in 1990.

It turns out that since --

CHAIRMAN CANTILENA: I'm sorry, sir. You're out of time.

Next speaker, please.

MS. COLEMAN: Good afternoon. I'd like to address you from three perspectives. First, as a forensic nurse.

In New York State, it is estimated that only 16 percent of women who are raped ever tell anyone. Even less than that seek medical attention.

How many women are missing the opportunity to prevent a pregnancy as a result of being raped because they don't go to a hospital?

Second, as an advocate, violence against women is a public health issue as well as crime victims issue. Access to emergency contraception is a public health service, as well as standard medical care following a sexual assault.

While New York State has finally passed legislation requiring all hospitals to have EC available on site to those rape victims who request it, this law does not benefit those victims who avoid or opt not to seek medical attention immediately after

being raped.

Making EC available over the counter will increase access to those thousands of women who opt not to go to the emergency department.

And, third, as a rape survivor, nine years ago I was tied to my bed, gagged, and raped at knife point. I know first hand about the shame, the humiliation, the degradation, the fear, the guilt, and the self-blame that rape victims go through.

It has been said by some that by providing emergency contraception over the counter this will decrease reporting of rape to criminal justice services. I disagree. It's the same, the degradation, the self-blame, and what victims have to go through when they disclose publicly, especially the perpetrator is someone famous, that decreases reporting.

Should these women also have to endure unwanted pregnancy because they choose not to speak out or not to seek medical attention in a public forum? I urge you on behalf of past, present, and future rape victims to please help increase this

access to a much needed public health service and to a standard of medical care.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Next speaker, please.

(Applause.)

MS. LEADER: Hi. My name is Alexandra Leader, and I'm 35 years old. I am co-chair of Red Stockings Allies and Veterans, a New York City based women's liberation group.

I got pregnant when I was 23. My boyfriend and I used condoms for birth control. I used condoms, and I still do, because I thought they were my best bet at protecting me from STDs.

After a year of us going out, the condom came off inside of me while we were having sex. I knew I was midway between my periods, and so there was a good chance I could get pregnant, but I decided not to get the pill that time because I heard it makes you throw up a lot, and also I was very busy and didn't want to take the time to wait at the doctor's office for a prescription.

Well, I got pregnant. The side effects of pregnancy were feeling tired and awkward for weeks and weeks until I could have an abortion, which then cost me over $400. A year earlier, I had led my NOW chapter in a campaign at the University of Florida to get a pharmacist fired for refusing to prescribe the morning after pill.

But even with my activist experience with the pill, I still didn't know that its side effects had been wildly exaggerated. I hadn't heard women talk about taking it like we're doing here today.

This is why women need to speak out from our own experiences with the morning after pill and birth control to find out what's really going on.

I have since taken the morning after pill six times over the course of ten years when my birth control did not work. It actually allows me to use condoms because it's my backup to a slipped or broken condom.

I now make sure I always have it at home. I've gotten it for free through friends in the health care professions. I've never thrown up and had little

or no side effects each time, and I haven't been pregnant again.

Twice I experienced mild jitters. That's it. And it's much cheaper with much less side effects than weeks of waiting and feeling like your body isn't your own if you get pregnant --

CHAIRMAN CANTILENA: I'm sorry, ma'am. You're out of time.

Can we have the next speaker, please?

MS. ALLINA: I'm Amy Allina from the National Women's Health Network. The network accepts no financial support from pharmaceutical companies and has no financial stake in Plan B or its competitors.

The network is here to urge the committee to recommend approval of the application to make Plan B available without prescription. Our brief comments will focus on consumer understanding and awareness of the product and how this affects the question of whether the prescription requirement can be removed while still insuring that the product is safe and effective for women.

Though EC has been known for decades to

prevent pregnancy after sex, it has not been widely used. Even with two dedicated products on the market and despite national education campaigns, awareness of EC in the United States is still low among women and among health care providers.

Because EC is not widely known to consumers, there may be concerns about whether women have enough information to use it correctly without the assistance of a prescriber.

The network has a longstanding commitment to insuring that women have good information about drugs they use, dating back to our earliest work advocating for the inclusion of patient information with oral contraceptive pills in the 1970s.

In the case of a nonprescription product, patient information is even more important. For a nonprescription product to be used correctly, consumers must be able without the assistance of a health care provider to understand the approved indication, any contraindications and safety concerns, and instructions for correct use.

We believe Plan B easily meets that

standard in actual use and label comprehension studies women have shown that most can understand the product information without the assistance of a health care provider. By including young women and over sampling women of low literacy in the studies and by amending the proposed labeling to respond to concerns about the understanding of those women, the company has provided additional assurance that women of varying ages and educational background will be able to use the product correctly.

Moreover, there's no additional information that prescribers or pharmacists are providing to women which would make EC safer or would make actual use more effective.

This is a safe and effective product, and --

CHAIRMAN CANTILENA: I'm sorry, ma'am. You're out of time.

The next speaker, please.

MS. JUDIE BROWN: Good morning. My name is Judie Brown. I am the President of American Life League. We represent over 350,000 American families,

and because my testimony includes as a backup all of the clinical information to which I will refer in my comments, I would invite you to read that.

Emergency contraception, first of all, is not contraception. So-called emergency contraception can by definition abort a child before that child implants. A human being begins at conception, not at implantation. Pregnancy begins at conception. It does not begin at implantation.

If a human zygote cannot implant, he or she will die. This means that the pills act to prevent pregnancy by aborting a child. For this reason alone the pill should not be available under any circumstance and certainly not over the counter.

The composition of Plan B, the particular brand of pill being discussed today, is such that two pills contain a lot of levonorgestrel, a chemical that can contribute to heart problems, circulatory problems, blood clotting, ectopic pregnancy, and more. There is more than adequate documentation in the medical literature to suggest that these pills are not only dangerous, but if given without access to a

complete medical history, potentially deadly.

As you are, no doubt, aware, a medical history is required prior to the dispensation of the birth control pill. Why isn't the same being required of the morning after pill?

Over-the-counter status immediately removes this safeguard. Who is going to be liable if a woman who ingests these pills suffers a deleterious side effect? It won't be the U.S. government.

Pills such as Plan B are designed with one purpose in mind: to destroy the evidence that a sexual encounter has occurred that could result in the conception of a child. The emergency in this case is a baby. If these pills are made available over the counter, adolescents who might have given such a result a second thought will not be inclined to take pregnancy into consideration before engaging in risky sex --

CHAIRMAN CANTILENA: I'm sorry, ma'am. You're out of time.

Next speaker, please.

MS. SEGUIN: My name is Stephanie Seguin.

I'm the Vice President of Gainesville, Florida National Organization for Women. I'm also the chair of the Florida NOW Young Feminist Task Force.

In 1999, I studied abroad in France. I was sitting outside late one night at a bar when these men rode up on bicycles wearing tee shirts that said "Help" in French. They were handing out condoms and packets of pills. I didn't know what the pills were. So I asked my host mother the next morning and in broken English she explained to me that it was the "if you think you might be pregnant and don't want to be" pill.

I figured it was the morning after pill I had heard of and was happily amazed at how easily you could get it. It made me think of the time I had needed the morning after pill here in the United States. My boyfriend at the time, who is now my husband, and I had had sex and the condom came off. The following morning, which was a Saturday, I braved the football game day traffic, which in Gainesville can be rough, to go to the campus infirmary which was closed. I had no idea where else I could possibly get

it. So I just crossed my fingers and hoped that I wouldn't be pregnant, have to drop out of school, and move back home with my parents.

How great it would have been if I could have just had it in my bathroom cabinet or ran to the local drugstore to get the morning after pill.

Women deserve access to the morning after pill any time, anywhere, and for any reason. And as for an age restriction, unwanted pregnancy is much more disruptive and dangerous when you're young. As a result of not taking the morning after pill when you're 14 means having a baby when you're 14. The morning after pill should be easily available to women of all ages, any time for any reason.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Next speaker please.

MS. BOGGESS: I'm Jane Boggess with the Public Health Institute.

Our organization in California has sponsored legislation to allow direct pharmacy access in that state. We currently have about 800 pharmacies

that provide EC and current usage suggests that we serve about 150,000 women a year.

Pharmacy access may look good from here, but remember that when it was first started, it was considered radical. Policy makers and others raised all kinds of concerns and worse case scenarios. None of them have come to pass.

Instead the EC pharmacy program in California and in other states -- and I'd like to note that the both Republican and Democratic governors have brought up EC pharmacy programs -- EC usage in California, direct access, has shown the tremendous need for this product.

Contraception fails at all times of the week, and often it's not consistent with access to a clinic or access to a doctor's office.

Despite the advances and successes, gaps remain in California. One million dollars later and still about a third of the rural counties don't provide emergency contraception.

Further, these programs have passed on costs to consumers. The pharmacists, rightfully so,

believe they should be paid for their time in providing the service. It's still a prescription setting in California, and this has been a prohibitive cost to many especially low income consumers.

While it has been helpful to have pharmacists involved, the bottom line is that in California we've always viewed this as transitional. State authority to expand access to EC is limited. It's both costly and very cumbersome to implement, and it's no substitute for federal FDA action.

In short --

CHAIRMAN CANTILENA: I'm sorry, ma'am. You're out of time.

Next speaker, please.

MS. HENRIQUEZ: Hi. My name is Silvia Henriquez, and I'm with the National Latina Institute for Reproductive Health, and we do not have any financial relationship with this pharmaceutical company or any others.

The National Latina Institute for Reproductive Health fully supports making Plan B available over the counter. We believe that the

availability of over-the-counter emergency contraception can play a dramatically important role in reducing unintended pregnancies, abortion, and sterilization rates among Latinas.

Additionally, it is likely to benefit an especially vulnerable population, namely, the disproportionately high numbers of young, low income, and underinsured Latinas with limited access to family planning and reproductive health care services, who may experience contraceptive failure or unprotected sexual intercourse.

We believe Latinas are a key constituency whose reproductive options could be greatly improved by the provision of over-the-counter emergency contraception. At present, accessing EC is made difficult for many Latinas who do not have a regular health care provider, are unable to take off from work within the 72-hour time horizon, and who cannot afford the cost of a health care visit in order to secure a prescription for emergency contraception.

Latinas face formidable obstacles to procuring reproductive health services. At present

the promise of emergency contraception is exactly that, a mere promise. Latinas are disproportionately poor and uninsured, and many must rely on understaffed, financially distressed public health institutions for their care, sometimes waiting weeks or months for an appointment.

Against this backdrop, it is unlikely that many Latinas will be able to access emergency contraception within the required hour time frame. Over-the-counter EC presents a safe and equitable solution that will enable many more Latinas and low income women to make use of this important reproductive option that can substantially reduce the number of unintended pregnancies and abortions in this country.

For these reasons the Latina Institute for Reproductive Health fully supports making Plan B --

CHAIRMAN CANTILENA: Thank you, ma'am.

Next speaker, please.

MS. VERA BROWN: My name is Vera Brown, and I'm a sophomore at the University of Florida. I'm also a committee chair for the Campus National

Organization for Women.

Last spring was my first and only experience with the morning after pill. As a college freshman, I wasn't able to have a child or afford the $500 needed to have an abortion. Luckily, a few weeks before that I had attended a Campus NOW meeting where I learned about the morning after pill, and I was told that it was available at my college infirmary.

The morning after pill didn't give me any side effects at all. In fact, I'm not on any birth control pill at all because they don't offer one birth control pill for a woman suffering from hypertension, as I do.

After hearing stories of other women who tried to get the morning after pill, I realized that I had a somewhat positive experience, but I also realized that it was through the feminists before me who fought continually to make sure that I had a positive experience, as you should.

But the problem that I have is what happens when I'm not a student anymore. What happens when I'm a mother, a professional, a grandmother?

Does that mean that I have to go through the same horror stories that I heard other women go through?

As a woman, I deserve equal accessibility to the morning after pill no matter what station in my life. Any compromise for a woman to have the right to get the morning after pill is discrimination of all women and her right to control her body.

Thank you.

(Applause.)

CHAIRMAN CANTILENA: Thank you.

Next speaker please.

MS. PETRAITIS: Hi. Good morning. I'm Carol Petraitis of the Clara Bell Duvall Project, and unfortunately the co-author of my paper, Wendy Bennett, was unable to be here today. She's seeing patients at Bayview Hospital in Baltimore.

But I'm grateful to be here to tell you about our study of community pharmacies in Pennsylvania, and we have no financial disclosures with the sponsor of the drug.

Our study was designed to determine knowledge and attitudes about EC among pharmacists.

We surveyed about ten percent of the pharmacies in Pennsylvania. The study was IRB approved, and it was published in Contraception this October.

Hopefully all of you received copies of it in your briefing packets.

Part of our motivation for conducting the study came from our work with rape victims. Many victims who visit emergency departments in Pennsylvania do not receive EC there, but leave with a prescription, and we wanted to learn how easily they could fill that prescription.

Of course, our findings apply to any woman seeking emergency contraception, whatever her reason.

Unfortunately our results were very discouraging. Sixty-five percent of the pharmacists that we spoke to said that they could not fill a prescription for EC that day. The majority, 79 percent reporting that the product was not in stock. Thirteen percent confused EC with RU-46, the French abortion pill, or abortion.

Six percent said that dispensing EC was against the store's policy. Seven percent said it was

against their personal beliefs, and finally, pharmacists in rural areas were much significantly less likely to be able to provide EC than those in urban areas.

In conclusion, our findings demonstrate that pharmacists pose a significant barrier to emergency contraception both for victims of rape, incest, and for women experiencing contraceptive failure.

Therefore, we strongly endorse the proposal to make emergency contraception available over the counter.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

Next speaker, please.

MS. GUBRIUM: My name is Erika Gubrium. I'm 30 years old and a member of Gainesville, Florida National Organization for Women.

I've been taking birth control pills for the last six years. Recently, however, due to financial difficulties, I decided to stop taking the pill.

Last month I had sex and the condom broke. This occurred during a vulnerable time in my cycle. So I was worried that I might get pregnant. Not having the money or time to see a doctor to get the morning after pill, I waited for my period, which was supposed to come within the next few days. It didn't come.

After several days I was even more worried. I had heard that home remedies, like taking a bunch of birth control pills could work in the same manner as taking one lower dose morning after pill. So I took several pills that I had left over from my prescription, which caused me to feel nauseous and irritable, and then I waited.

A week later, with extreme relief, I got my period. I can't imagine what I would have done had I been pregnant. As a full-time Ph.D. student, I'm also working three jobs just to pay my rent. I can't afford to have an abortion right now, much less have a child.

Because of lack of access and the well kept secret of how the morning after pill works, I was

forced to come up with my own homemade remedy. As I see it, the only difference between taking a pill once a day every day and taking a pill once after contraceptive failure or unprotected sex is that a woman like me doesn't have to hand over half her paycheck to buy a daily birth control pill or schedule an expensive appointment with a doctor to protect herself from an unwanted pregnancy.

Based on my experience, I can tell you that requiring women to get a prescription for the morning after pill poses severe obstacles to its availability. Women must have unrestricted over-the-counter access to the morning after pill.

Thank you.

CHAIRMAN CANTILENA: Thank you.

Our next speaker, please.

MS. STANEK: Hi. My name is Jill Stanek. I'm a registered nurse with ten years' experience, the bulk of which is in the hospital labor and delivery department.

I'm here on behalf of Concerned Women for America.

I'm focusing my testimony today on the disastrous effects that ECs would have to minor girls if they were made available without prescription. Because there have been no long-term EC studies performed, endorsement of their over-the-counter use by the AMA, ACOG, and Family Planning Centers must be to thwart getting sued for not providing informed consent. I can see no other logical reason why responsible physicians would intentionally forego the opportunity to assess, diagnose, treat, and educate their patients.

There is significant potential for abuse and misuse of ECs. Making ECs available would be a welcome tool for adult sexual predators who molest family members, children of friends or students. They could keep a stash in their bedroom drawer or their pocket to give their victims after committing each rape.

Alan Guttmacher Institute reported the younger women are, when they first have intercourse, the more likely they to have had nonvoluntary sex. Planned Parenthood reported teenager girls with older

partners are more likely to become pregnant than those with partners close to their own age.

NARAL identified the link health care professionals provide girls who seek EC use. They stated, "The need for emergency contraception can bring young women into family planning centers where they can receive other health care services and counseling."

Dr. Jocelyn Elders co-authored a commentary in JAMA that said, "Pregnancy may be the sign of ongoing sexual abuse." She concurred with Planned Parenthood --

CHAIRMAN CANTILENA: I'm sorry, ma'am. You're out of time.

Next speaker, please.

MS. GANDY: My name is Kim Gandy. I'm President of the National Organization for Women, and we have no financial interest in this proceeding.

Our organization has for nearly four decades advocated and supported the wide availability and accessibility and affordability of all forms of safe and effective contraceptives. Therefore, it is

our very strong urging that these committees recommend to the Food and Drug Administration that they make emergency contraception available over the counter.

As its name suggests, this is about responding to emergencies, emergencies that are the result of unprotected sex or contraceptive failure. Making Plan B available over the counter would significantly reduce the stress and trauma experienced by women in these emergency situations while preventing thousands of unwanted pregnancies.

You've already heard from several of our activists about their experiences in the United States and abroad.

EC is not only a safe and effective method to prevent unwanted pregnancy. It can also empower women who have been raped with a sense of control and provide an important means to help them cope with the trauma of sexual assault.

In one survey when calls were made to health providers during business hours, only three out of every four attempts to obtain emergency contraception resulted in appointments or telephone

prescriptions within the key 72 hours. Because EC is more effective when it's used earlier and most effective within 12 hours, these obstacles pose a serious threat to women's health.

Women need to have access 24 hours a day, seven days a week.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

Next speaker please.

MS. McGRAW: Thank you very much.

I'm Deven McGraw of the National Partnership for Women and Families. We're a nonprofit, nonpartisan advocacy organization that promotes quality health care for women. We have no financial interest in Plan B, the sponsors, or these proceedings.

I can't speak to the interest of Hugh Hefner, young playboys or sexual predators in these proceedings, but I can tell you that the women we represent are very much in support of making Plan B available over the counter for two primary reasons. One is the access issue, which has been discussed a

lot. So I won't use my dwindling time here to go into that.

But the one I want to draw attention to is the issue of increased opportunities for education. I have two postgraduate degrees. One of them is a Master's of Public Health. I've been fortunate enough to always have a regular health care provider. Until I started doing work on this issue for my organization, I didn't even know about emergency contraception.

If you make Plan B over the counter, it will provide a significant, quite frankly, financial incentive for the sponsors to educate women both about how this product is to be used, what is the mechanism of action, what are the side effects, if any, what are the contraindications, which as far as I can tell are none, and how its appropriate use as a contraceptive device for emergency purposes.

The other thing I want to speak to is this notion that if you make it available over the counter it will somehow be misused or abused by women, and quite frankly, we think that that is both insulting to

women's intelligence and mischaracterizes how they make reproductive health care decisions.

We trust women to make decisions about use of over-the-counter medications, both for themselves and for their families, including children, for a range of products for which the side effects and the potential adverse effects for misuse are much more serious than those for Plan B, and we encourage you to judge this product based on those same standards as you would for any over-the-counter medication, based on the scientific criteria.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you, ma'am.

(Applause.)

CHAIRMAN CANTILENA: Next speaker, please.

MR. ULMANN: My name is Andre Ulmann, and I'm the CO of HRA Pharma. We have no business relationship with Barr.

HRA Pharma is the French pharmaceutical company which has registered Norlevo, a levonorgestrel only emergency contraception, in over 50 countries.

Norlevo's first registration in France in May '99 was soon followed by a switch to a nonprescription status, a move subsequently made by a majority of European countries.

In all but two of these countries Norlevo is delivered by pharmacies without prescription. Only in Norway and Sweden is Norlevo available directly over the counter.

Today women in 27 countries worldwide can obtain Norlevo without a doctor's prescription, which corresponds to over 27 million women of childbearing age in Europe and a total of nearly 80 million women worldwide. As part of a country that facilitated the use of Norlevo, especially in nonprescription settings, HRA Phara recently obtained approval for administration of two tablets in a single intake.

Here we wish to make public information that confirms the safety of nonprescription emergency contraception which is presented by Dr. Erin Gainer.

DR. GAINER: My name is Erin Gainer. I am in charge of research and development at HRA Pharma.

Our post marketing safety database now

contains information on over seven million levonorgestrel emergency contraception treatments, and all of the periodic safety update reports filed since first registration have concluded that the benefit-risk ratio is positive.

In addition, HRA Pharma has undertaken a series of studies to evaluate the process and outcomes of this switch to nonprescription status. A retrospective prescriber based study in France confirmed the safety and efficacy profile of Norlevo in real world use. French, Norwegian, Portuguese and Swedish women interviewed following use of Norlevo on a nonprescription basis confirmed that they were able to diagnose their need for emergency contraception understand how to use it and comfortably manage any side effects.

Furthermore, these users expressed their comfort with and praised the practicality of nonprescription access to emergency contraception. Ongoing research will assess the experience and practices of emergency contraception users during the six months following dispensation in a pharmacy.

Emergency contraception has been held as one solution to prevent unwanted pregnancy and pregnancy termination. HRA Pharma has been closely following abortion figures since Norlevo launch in European countries.

Recent official statistics from Finland show a six percent decrease in pregnancy terminations in the first half of 2003 as compared to the same period in 2002, with the largest decline of about ten percent of parented women under 20 years of age. According to a Finnish official, the decrease in abortions is likely a consequence of, among other things, the fact that emergency contraception has been available in pharmacies without a prescription since May of 2002.

We testify today to the consistently positive benefit-risk profile we have observed over four years of experience with nonprescription access to Norlevo emergency contraception.

CHAIRMAN CANTILENA: Okay. Thank you.

Next speaker, please.

MS. CHURCHILL: Hi. My name is Candi

Churchill. I'm with Gainesville Women's Liberation out of Florida, and I have a display with them, not yet.

Some argue that -- not yet. Oh, well -- some argue that making the morning after pill over the counter like aspirin and cold medicine is going too far and although the morning after pill is safe, women should be able to obtain it only through a pharmacist prescription.

I disagree. The morning after pill should immediately be made over the counter, and it should be affordable and accessible to women of any age, particularly young women.

The United States should follow the lead of at least 37 other countries which already provide women access to this safe backup birth control method without restriction. The science and the studies have been done. It's time to catch up with most of the world.

Requiring women to reveal the details of sexual activity to a pharmacist who may be a stranger, or worse, a friend of your family, is humiliating and

unnecessary. Women should be able to have the morning after pill around before a problem arises.

Will pharmacists be willing to give women the woman after pill just in case? Some will; some won't. It shouldn't be in their hands. It should be in the hands of women.

In 1991, a pharmacist at my college, the University of Florida, refused to dispense the morning after pill. If over the counter women will make sure we have a current dose in our medicine cabinets at home for ourselves and friends who need it, just like women have other medical supplies for their families.

Finally, we should be able to send a man to pick up the morning after pill. After all, they're at least half of the problem that we're in this situation.

(Laughter.)

MS. CHURCHILL: The only way a man can go pick it up for us is if it's over the counter.

I hope you will vote to make the morning after pill over the counter. Women will settle for nothing else.

Thank you.

(Applause.)

CHAIRMAN CANTILENA: Okay. Thank you.

The next speaker, please.

MS. TAYLOR: Hi. My name is Jennifer Taylor, and I'm the Director of Communications for Human Life International, an international educational postulant, and I'm prepared to read a statement today, but it's in your packet and I'll let you read it, and instead I decided to speak from my heart.

Most of the women who have spoken here today from the National Organization of Women and other groups have said they obtained the pill from the recommendation, encouragement, and sometimes even pleading of their physician, admitting the benefit of having access to such a physician. And some of these women even said, "And thank God for these doctors."

Yet they're asking you to keep other young women from the advice they might otherwise receive from their physicians.

Also today we've heard a lot about the failure of the condom. In fact, I think every one of

these young women mentioned the condom failed them. Yet the organizations these young women represent are the same organizations that applaud the condom and work overtime to make it available in such places as Africa where HIV and AIDS rates are only increasing. Do they think the condom works better in Africa?

My point: these young women have very touching testimonies. Their emotion behind their stories may want to make you, incline you to support over-the-counter use of Plan B.

Another common thread that runs through these stories is the inability to control themselves in sexual situations. As a young woman how sad it is to know that these women are slaves to their bodies and that the organizations they represent lead them to believe that they themselves cannot control themselves, but have to rely on pumping themselves full of drugs.

I am 30 years old and I've been married for two and a half years. I don't believe in contraception, and I don't use it, and I've never been pregnant, and my husband and I don't abstain as much

as people might want to make you believe they do when it comes to NFP.

I've been taught natural family planning, and I know how to use it. I'm the one who's truly free because I'm not on the pill. I'm not a slave to my body, and I'm not a slave to the ideology of any organization. I don't have the stress and the worry and the anxiety that these other young --

CHAIRMAN CANTILENA: Okay. Thank you. I'm sorry. Your time is up.

Next speaker, please.

REV. TILLER: My name is Reverend Robert Tiller, and I represent the Religious Coalition for Reproductive Choice.

I have no financial relationship with Plan B or other conflict of interest to disclose.

The coalition is a 30 year old organization whose members include agencies of the Episcopal Church, Presbyterian Church USA, United Church of Christ, United Methodist Church, Unitarian Universalist Association, and Reform and Conservative Judaism.

There's broad consensus that unintended pregnancy is a serious public health problem, that it has a negative impact on family life, and that reducing unintended pregnancy will strengthen families.

Emergency contraception has been proven to be a safe and effective way to reduce the rates of unintended pregnancy, and we urge the FDA to approve this application.

Objections to this application come from groups opposed to abortion because of their own particular religious view that a fertilized egg is a person. Their objections can be ignored because it has been shown that emergency contraception does not cause abortion.

These groups also claim that women cannot be trusted to use EC without supervision and that EC causes promiscuity. Such claims are not only unfounded, but they also deny that women can make moral decisions, and they attempt to incorporate narrow religious views into health care regulations that affect us all.

Currently obstacles in the health system hinder women's ability to decide in a timely fashion whether to take EC or not. The role of the FDA after ascertaining the safety and efficacy of this drug should be to remove unnecessary barriers to its access. Women must be trusted to make moral decisions about its use according to their own beliefs and circumstances.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

Our next speaker please.

DR. THOMAS: Amen, Reverend.

My name is Albert G. Thomas. My specialty is OB-GYN. I'm a member of PRCH, Physicians for Reproductive Choice in Health, and we have no financial interest.

I strongly encourage the U.S FDA advisory panel to grant over-the-counter status to emergency contraception pills. Given the unacceptably high annual number of three million unintended pregnancies every year, the extensive scientific research in the efficacy of EC, and my own clinical experience of

almost 19 years, I believe that the over-the-counter availability will remove unnecessary and harmful barriers of a highly effective, entirely safe product that has proven integral to decreasing the U.S. abortion rate.

I am an attending physician at Mount Sinai Medical Center in New York City. Just two weeks ago a 25 year old patient came to me for routine yearly exam. At the end of her exam, she thanked me for being her doctor. I asked her why.

She then related a story that occurred on a Sunday morning that January, last January. At that time she experienced a condom break at 3:00 a.m. She called me, and of course, I called the pharmacist who dispensed the medication from one of New York City's all night pharmacies.

She then proceeded to explain that she was hesitant to contact me at that late hour. I repeated my usual spiel about sleeping near the telephone with high expectations of receiving calls from pregnant and laboring patients, in addition to patients with reproductive emergencies, especially broken condoms.

I then began to consider the nearly three million women in the U.S. who didn't call their physician, who became pregnant against their wishes under similar circumstances, who chose to have an abortion or who felt forced to make the heart wrenching decision to give the unwanted child up for adoption.

Imagine the impact of unfettered access to EC in all of those couples. Imagine their avoidance of emotional stress that will result when a woman is allowed to walk into any pharmacy and obtain this postcoital contraceptive with any of our permission. I hope that you, the Advisory Commission experts, will heed the medical and scientific data strongly suggesting the increased EC access will decrease death resulting from pregnancy related complications. This fact alone should establish over-the-counter availability of EC for all women as a crucial public --

CHAIRMAN CANTILENA: Okay. Thank you very much.

That concludes the open public hearing.

I wish to thank all of the speakers for staying on time, and I apologize to the ones who we had to cut off for time.

We will now break until 2:00 p.m., an hour and eight minutes for lunch. Just before we go to lunch, let me remind the committee members to refrain from discussions of the topic of the meeting during lunch, and any committee members who want to go to the back door of the restaurant, please gather up here at the head of the table.

And the committee members are having lunch in the Tack Room, and if you come up here, we'll show you how to get there.

Thank you.

(Whereupon, at 12:50 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m.)

AFTERNOON SESSION

(2:01 p.m.)

CHAIRMAN CANTILENA: Okay. Let's go ahead and get started if the committee members can please take their seats.

This afternoon what we plan to do is start out by allowing the committee to ask clarifying questions of the sponsor or FDA for issues that have come up during the morning, and I would ask the committee members to hold themselves to one question each time on each round, so to speak, so that everyone has a chance to speak.

Then after we do the clarifying questions, we'll have a general discussion about the safety and the actual use studies, and then we'll actually go to the questions for the committee at the end.

The format for the questions for the committee will be that everyone has a chance to answer individually and explain their answers either way so that you'll all have a chance to comment on each and every question, and I know that does add some time, but I think that's very important in terms of what the

FDA is hoping to gain from this committee meeting.

So let's first open it up for clarifying questions for the sponsor and for FDA that have to do with the safety of the switch.

Yes, Dr. Uden.

DR. UDEN: During one of the presentations we had by Daniel Hussar, he talked about the pregnancy X status or what is the status of this product in terms of pregnancy?

CHAIRMAN CANTILENA: That's for FDA.

DR. GRIEBEL: I'll start the answer, and then I think Dr. Kweder will want to add on.

The current prescription Plan B labeling includes information on pregnancy. There is under precautions a subsection, "pregnancy." It does not have a so-called pregnancy category assignment, and in fact, we have a guidance that we're working on where we are removing pregnancy category assignment to the oral contraceptive labeling.

I think Dr. Kweder may want to follow up.

DR. KWEDER: I think Donna has covered it.

The reason for that is that the only

reason that the oral contraceptives carry pregnancy Category X, which is that not because they are a risk; it's only because you wouldn't intentionally use an oral contraceptive if you knew you were pregnant. And so it's really a quirk of the regulation and how they're written that they have the Category X.

We've endured a great deal of criticism from the medical community about having that category on oral contraceptives, and so as Dr. Griebel stated, we're going to be removing it and just putting information about what to expect or to be concerned about, if anything, should an exposure in pregnancy occur.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Lockwood.

DR. LOCKWOOD: I actually had a guess, I guess, for both the FDA and the manufacturer about the labeling specifically as regards breast feeding. It says, "If breast feeding, ask doctor before use," and I'm unaware of any literature whatsoever that even long-term progestin only contraceptives have any ill effect on breast feeding. In fact, they seem to have

some beneficial effects in breast feeding.

Certainly there shouldn't be any beneficial effect whatsoever from a short course like this. So why is the labeling there?

DR. GRIEBEL: Could I clarify? Is that in the prescription label or is that -- it's in there. Okay. Dr. Ganley just sidebarred me and told me that that is actually required labeling for an OTC product, but we would be interested in hearing your comments on whether you think it's necessary.

DR. LOCKWOOD: No.

(Laughter.)

CHAIRMAN CANTILENA: Well, thank you for being brief.

Any further questions concerning clarifying? Yes, Dr. Hager -- I'm sorry. Dr. Clapp first.

DR. CLAPP: My question was about breast feeding, the same question. But I would add that as a pediatrician who receives those calls all day and night, I don't think it's necessary to include it on the labeling because it, first, suggests to the

potential buyer that there is a reason for concern, and I don't think there is.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Tinetti.

DR. TINETTI: -- or for the sponsors, and it has to do with safety to the fetus and/or child if there is a pregnancy, and for the packet there was some illusion to the fact that there hasn't been any identified problems with it, but I guess my question is how systematic has been the evaluation and follow-up of pregnancies that come to birth and safety in that population.

DR. DAVIS: I can just say that it is extremely difficult to get accurate data on pregnancies and their follow-up with exposure to literally any drug, but certainly to your, you know, contraceptives, steroidal hormones.

Now, we do know from large epidemiologic studies with oral contraceptives where women have taken the oral contraceptive literally for three months in the beginning pregnancy, and there has been no hard data that has shown an association or risk

factor with oral contraceptives taken for several weeks or months in a pregnancy.

And there is no data that I'm aware of of a teratogenic risk with levonorgestrel only from oral contraceptives or emergency contraception.

CHAIRMAN CANTILENA: Other comments from the sponsor?

(No response.)

CHAIRMAN CANTILENA: Okay. Dr. Hager.

DR. HAGER: Yes. I have a question about the self-diagnosable aspect which is one of the indications as far as going OTC. It would be my contention that the diagnosis is not unprotected intercourse, but rather unprotected intercourse just prior to and at the time of ovulation.

So my question is are there data available on the unnecessary uses. Does the sponsor have any information? Does the FDA have any information about how excessively used this product is beyond that window?

DR. GRIEBEL: We're not aware of any. I don't know if the sponsor has.

CHAIRMAN CANTILENA: Okay. If you can use the microphone at the podium.

DR. BEN-MAIMON: Can I have Slide 543 please?

What you can see here is that in some countries Plan B is actually approved or levonorgestrel emergency contraception in these doses is actually approved for postcoital use in women who are of low coital frequency, and that's defined as less than four times a month. And so you can see in over 2,800 women and over 13,000 cycles in 14 studies, there's a good bit of data.

There's been only one ectopic reported. There have been no serious adverse events, and these women have taken up to ten tablets per cycle.

With regard to the issue of ovulation and taking it around ovulation, could I have slide 375, please?

You can see from this slide, and this is by Dr. Croxatto, they looked at when women ovulate and what day of the menstrual period, and clearly predicting this is very difficult and can occur

anywhere from day ten all the way out to day 23.

In addition, there have been studies done looking at women in consecutive cycles, and it's almost impossible even from consecutive cycles to predict when women are ovulating.

And so if people are taking it based on a calculation of when they anticipate their menstrual period, there's a lot of risk and they really could become pregnant inadvertently.

DR. HAGER: Which basically means that the recommendation is to take it with every act of unprotected intercourse; is that correct?

DR. BEN-MAIMON: That's correct.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Trussell.

DR. TRUSSELL: Another direct answer to that question, Dr. Hager, is that we recently published a paper where we compared the risk of pregnancy by cycle day relative to ovulation, and it is true that there's only that six-day window, but when you then convert that into the risk of pregnancy by cycle day where cycle day one is the first day of

bleeding, then there is no day except for the first two days where the risk of pregnancy is zero.

And of course, the problem is that since women don't know when they're ovulating, the only guide they have to go by is cycle day measured in the normal way, not relative to day of ovulation.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Giudice.

DR. GIUDICE: I don't know if we'll get to this at some other time, but in terms of in the actual use study, there was for the lower literacy group a 46 percent comprehension or reporting by reading the package that this would be used for contraception, not necessarily for emergency contraception.

And at some point are we going to be talking about the print in the package?

CHAIRMAN CANTILENA: Yes, that will come up later.

DR. GIUDICE: Okay. Thank you.

CHAIRMAN CANTILENA: Okay. Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I wanted to get some

clarification on the Washington State experience with the pharmacist. I don't know who brought this up. I don't remember, but I'm trying to get some clarification of what were, in that survey, what were the number one reasons, other than the contraindication of vaginal bleeding or that the patient may suspect that she was pregnant that the pharmacist gave when they didn't give the emergency contraception?

DR. BEN-MAIMON: When they did not?

DR. MONTGOMERY RICE: When they did not give the woman the emergency contraception.

DR. BEN-MAIMON: That was in the actual use study actually, and in that study women came in -- and can I have Slide 389, please, or the ones we looked at this morning? -- the women came into either the pharmacy or to the clinic, whichever was the appropriate place, and basically said, "I had unprotected sex, and I need emergency contraception."

And I would like to clarify from this morning there was a question about counseling. These women received no education at all. They basically

were given the product, asked to read the drugs facts panel. It was sealed, and then they made the decision whether or not they wanted to use the product or not.

And if they thought the product was appropriate for them, they were then told that they had to sign an informed consent. And what happened here is I don't know if you remember, but there were 663 patients, and there were the 500-plus that were in the trial, and then there were the 80 that were not enrolled.

Eleven of these did not meet eligibility criteria, and that was why. Of the 69 who would not sign an informed consent, nine actually received nothing. They walked out with nothing.

Two received other medications, such as Lo/Ovral or Ovral, and 58 got a prescription for Plan B. The reasons were that they did not meet the eligibility criteria, which included that they had to speak English because the packages were in English. They had to be willing to be followed up. They had to be available and/or that they would not sign an informed consent. And clearly, for those women we

don't have a lot of information.

But what I can tell you is in this 58, of the women who provided us information, the vast majority wanted additional information, and because it was an actual use study, we couldn't provide the additional information prior to signing the informed consent.

So they sought additional information, and then with that additional information they got Plan B.

DR. MONTGOMERY RICE: I guess I'm trying to get outside of sort of a study, that when you look at surveys from like, let's say, the California experience have you done any surveys of those pharmacists and what the percentage of them actually filled a prescription and what reasons they give that they don't fill the prescription? Do you have any of that type of information?

DR. BEN-MAIMON: We don't have quantifiable data, but we do have anecdotal data which says that a lot of them don't fill the prescription. One, they don't have it. It's not stocked because, again, remember from Washington, the pharmacy access

programs, only 26 percent are actually participating in the pharmacy access program.

So many pharmacies don't either stock it still and are not participants and, therefore, can't dispense it.

The women may not meet the criteria. They actually have to go through a questionnaire, and the other thing is that the pharmacist chooses not to dispense for whatever reason.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Crockett.

DR. CROCKETT: Thank you.

First I'd like to start by saying thank you for being a company that's concerned about lowering the induced abortion rate, and you should be applauded for that. That's a wonderful objective.

We've had a lot of discussion or some discussion about the low literacy groups and their comprehension, and I agree with those concerns, but I wanted to raise another issue, and that is my high literacy group.

We heard from some of them in the open

public hearing this morning, and although your labeling labels this as an after intercourse or emergency contraception, several of them indicated that they would want to use it as a primary form of birth control because they didn't want to use other forms of birth control.

In addition, my high literacy population of patients smart enough to figure out that this is not just Plan B, an indication coming over the counter; it's a drug, levonorgestrel, which is a progesterone, which can be used for lots of other things. There are women that use it for menopausal symptoms. There are women that use progesterone for luteal phase defect, when they're trying to get pregnant and infertility issues, and it's not going to take them very long to figure out that levonorgestrel is now over the counter and they can go get it, and that raises a lot of concerns for me.

In your handouts to us, you indicated that one of the ways that you wished to consider controlling how this was dispensed was by pricing it high enough so women would not use it as a regular

contraceptive or as a progestin only contraceptive, and I wanted you to address that a little bit because I'm wondering how you plan on handling these concerns about the high literacy group and about how you could raise the price high enough to not preclude our lower socioeconomic group from having access to the medication at the same time.

DR. BEN-MAIMON: I think there's two responses. First of all, there's really two deterrents to using this for routine use. One is the menstrual irregularities associated with it.

The studies that I showed you earlier in women of low coital frequency where they are using it is routine birth control. The reason it was never pursued in this country, in particular, is because there are so many menstrual irregularities, and we all know women don't like to bleed irregularly. They like much more a predictable time for bleeding.

And so that in and of itself, I think, worked as a deterrent.

Second of all, I don't think that we're talking about using price as a deterrent. I think

though that just given the circumstances, the fact that one package -- first of all, it's a single use package as you saw -- one package is comparable in price to one month's worth of oral contraceptives.

And so clearly repeated use is difficult, and as we did hear in the public hearing, many of these people who are using -- many of the women using it are on a budget. They are either in school or going through school or newly in jobs, and so price, although I don't think we intend to utilize it as a deterrent, may very well act that way.

With regard to the lower income women, we will be providing it, as we said earlier, to clinics at a discount, and so it will still be available in clinics to women who cannot afford private practice or who don't have medical insurance.

CHAIRMAN CANTILENA: Okay. Just a quick follow-up.

DR. CROCKETT: I would just like to make a statement to the FDA that I disagree with using pricing as a manner of controlling how a medication is dispensed over the counter. That's not a reliable

mechanism.

CHAIRMAN CANTILENA: Thank you.

Dr. Benowitz, please.

DR. BENOWITZ: This morning there were two safety concerns raised that I would like to ask a question about. One was if Plan B was to be used repetitively for a long period of time, and the second was use in adolescents.

The first question which could be FDA or sponsor or the panel, because I'm sure you know better than I, is a summary of the safety data on just progestin only contraceptives. We've had a lot of experience with that, used for years and years and years, and I think that would be useful for me to know.

And the second thing is: are there any studies of progesterone in adolescent animals to look at development or to look at brain development and look at behavior as there are for other sorts of drugs?

DR. DAVIS: Dan Davis for the FDA.

I certainly can address the question about

the repeated use. All of the clinical data that I presented was levonorgestrel only. None of that was from combination oral contraceptives, and we have studies that go back to the '70s and '80s where they really were doing dose ranging to find out what dose would be most effective for levonorgestrel starting at .15 milligrams and going up to one milligram. And those were for women using the levonorgestrel after intercourse on a regular basis for regular postcoital contraception so that we have thousands of women who use the varying doses on repeated.

Probably the best day or one of the best data was the Kesseru study from Lima with over 2,800 women for an average of nine months using the .4 milligram dose for an average of nine times per month. So if you multiply the .4 by nine, you get 3.6 total dose every month for an average of nine months.

That study actually went up to 25 months. So we do have, you know, some participants who used that dose up to 25 months.

For adolescent studies, I would simply say I'm not aware of a study that has been published for

adolescent use, but perhaps the sponsor has some more specific data on that issue.

DR. BENOWITZ: Can I just ask a follow-up?

The other question is just for the ordinary progestin daily use oral contraceptive, what's the safety profile for that?

DR. DAVIS: Extremely high. The only issue that has been raised is that of ectopic pregnancies with the progestin only daily contraceptive pills, and the incidence there, although it appears to be higher, it's not higher than what we would expect in the general population, and that's why I presented the data on ectopic pregnancies from the randomized clinical trials for levonorgestrel specifically for emergency contraception.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Lockwood or are you satisfied, Neal?

DR. BENOWITZ: I just wondered had the sponsor looked at the question of progestins in adolescent animals.

DR. BEN-MAIMON: No, we had not.

CHAIRMAN CANTILENA: Okay. The answer was

they had not.

DR. LOCKWOOD: I don't want to use up my question, but I want to help answer his question because my NIH grants are on this topic. So I have some knowledge of this area.

Depo-Provera and the implantables, particularly Depo, are associated with a higher rate of osteoporosis, and most of these women develop abnormal uterine bleeding. There's about a 15 pound weight gain on average after use, and there's a higher rate of depression. So those are the long-term consequences.

But that was not my question. If I could beg you to put back up the slide that showed the pattern of ovulation, and the question I'm going to ask is as follows.

We know from the published literature that the earlier in an ovulatory cycle prior to ovulation that the drug is used, the better the contraceptive effect and the greater the likelihood of ovulatory either dysfunction or frank disruption.

My question to you is: do we have data on

the efficacy of the agent after ovulation? So, for example, if a woman ovulates on day 14 and she has unprotected intercourse on day 17 and uses this agent, what is the likelihood of her being pregnant? It should be eight percent or so if the drug had no effect.

DR. BEN-MAIMON: This is actually very difficult to do. Obviously in randomized trials you can't randomize women to get pregnant or not, and so the studies that have been done are complex. The only real data post ovulation besides the statistical data generated by Dr. Trussell is that there is clear data in the Kesseru by Kesseru that the sperm motility, the cervical mucous, as well as uterine pH, change within hours of taking levonorgestrel, but the connection between that and an impact on fertilization has not been shown.

There have been some very early studies on combination therapy, and I think that's really important that there may be some changes in the endometrial lining, but again, that's combination, and when you give estrogen and progesterone, as you all

know, the ratio is highly important in maintaining t he integrity of the endometrial lining.

And there are really no studies to date that have been published that show that levonorgestrel has any impact on the endometrial lining post ovulation.

In addition to that -- can I have 362? -- again, estrogen containing products are of limited value because of the impact of estrogen. As somebody said earlier, progestin traditionally is used to maintain the integrity of the endometrial lining, and is used in women with a luteal phase defect just for that purpose.

In addition, anti-progestins, such as RU-486 or mifepristone, are detrimental to the endometrial lining. So, again, anti-progestins work to destroy the endometrial lining, not progestins.

And so clearly, the only real evidence of how levonorgestrel works is that it prevents ovulation; it impacts sperm motility and sperm migration through changes in the cervical mucous and the pH, and there really is no data to suggest that

there's any impact on implantation or fertilization.

DR. LOCKWOOD: Just a point of clarification. When one gives progesterone for luteal phase defect, you usually begin it around seven days after ovulation. You don't begin it in that immediate periovulatory period.

I raise the issue because of obviously the issues of whether this is a contragestive or contraceptive, and also because we know that progesterone given at around the time of attachment can affect HOXA-10 expression. It can affect integrin expression. It can affect Lith expression by endometrial glands, et cetera.

So the issue becomes not does it necessarily create a hostile environment in the endometrium such that you would be able to affect advanced implantation because I agree with you. Progesterone is good, not bad to do that.

But the issue becomes does it affect attachment, and does it act, in other words, like an IUD rather than an anti-fertilization agent. And it sounds like you're telling me no one has done the

studies, and I couldn't find any that at least I could discern from a Medline search or from looking through your data.

DR. BEN-MAIMON: The studies are not available. The biggest issue here though is that Plan B or levonorgestrel only emergency contraceptions work like other oral contraceptives in that way, and so especially progestin only containing oral contraceptives, and so the data is clearly there's no data that's definitive in either way.

But, again, I think logic precludes us from assuming that that's the mechanism of action.

CHAIRMAN CANTILENA: Okay. Dr. Stanford.

DR. STANFORD: I'd like to offer a little bit of a different opinion on that issue, and I think it is an important issue for women who want to have a clear idea of the best evidence of how this works and for their informed consent for use.

I don't think it's quite as clear-cut as has been presented that there's no data on one side and all data on the other side. If you look through all of the studies we have got in our background book,

there's data on both sides.

But I don't think we have time to discuss all of the nitty-gritty, but I would like to point out what I think is probably the most to date compelling piece of data on the side that says this may work after fertilization at times, and that is the data that it's effective up to four or five days after.

Now, I understand that it's not being proposed for that indication, but there are certainly people proposing that use based on studies showing that, yes, the effectiveness is less the farther out you go, but there's still fewer pregnancies than you would expect, and the pregnancy rate is still lower than the expected pregnancy rate of four or five days in a couple of studies, including the World Health Organization 2002 study we have here where it was estimated at 60 percent effective four or five days after.

So when you understand that there's five or six days where intercourse can result in pregnancy and you've got five days, four or five or even three days after administration of a drug after intercourse,

there's certainly a good percentage of those times when it's being given after ovulation because you've got a five-day window of giving it and you've got a five-day window when intercourse can result in pregnancy.

PARTICIPANT: Before or after ovulation.

DR. STANFORD: Right. You've got a five-day window where intercourse can result in pregnancy up to the five or six day up to day of ovulation, depending on which study you look at. Studies that have adjusted for uncertainty and timing of ovulation have suggested it may have even been five days rather than six.

But anyway, so you've got this five or six-day window and then you've got a five-day window where it is shown to be effective. There's no way that -- you know, there's certainly some epidemiologic evidence from there that suggests that it is working after fertilization some of the time, and I think it is misleading to say we have no suggestion of that happening.

CHAIRMAN CANTILENA: Okay. How about if

we go forward from a comment from Dr. Giudice and then Alfano?

DR. GIUDICE: Actually I have two comments. One is that a five-day window can be interpreted with the sperm being in the reproductive tract for 72 to 96 hours with a very late ovulation and with an effect of the levonorgestrel on a decreased release of the sperm in the cervical mucous or in the crypts of the fallopian tubes.

Secondly, for fertility therapy we commonly begin progesterone administration on post ovulatory day 2, and for infertility therapy with embryo transfer, we commonly begin supplemental progestin or progesterone one day before embryo transfer.

So I just want to make it very clear that administration of progesterone clinically early and periovulatory has no significant impact upon implantation rates.

CHAIRMAN CANTILENA: Okay. Dr. Alfano.

DR. ALFANO: Yes. I think this question is for Dr. Chen.

And I realize that the ADR rate is very low for this drug, but my question is: have you been able to discern any differences in ADRs in jurisdictions where the product is available with an Rx or without an Rx, be they countries or states?

DR. GRIEBEL: No, we haven't been able to do that.

CHAIRMAN CANTILENA: Okay. Dr. Macones.

DR. CHEN: Yeah, we actually compare with --

CHAIRMAN CANTILENA: I'm sorry. I thought that was the answer.

DR. CHEN: Oh.

CHAIRMAN CANTILENA: Is that the answer or is there more data? There is no more data. Okay. So it was just a reinforcement of the answer.

Okay. Please proceed.

DR. MACONES: Just a question about the actual use study. As I recall from the numbers that you presented, 40 percent or so of the participants had used emergency contraception before, and I was wondering if the 670 percent who hadn't or who were

first time users had similar performance, proper performance, compared to the other 40 percent who were second time or more users.

DR. BEN-MAIMON: That is correct. In the actual use study we did have 40 percent of the women who did use the product before, and 412, please. And what you can see here is contraindications. Remember they were pregnancy, unexplained vaginal bleeding or allergy, prior users versus naive users. Incorrect use was similar in both groups.

And you can see this was taking the first pill within the first 72 hours and taking the second pill at 12 hours exactly were very similar. So there was no difference in the two groups.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Lam.

DR. LAM: In the actual use study, 32 percent of the users did not take the second pill correctly. Just a point of clarification. Did the sponsor follow up with those 32 subject or 32 percent of the subjects to find out why they failed to follow that relatively simple instruction?

And what type of strategy would the sponsor propose to improve that adherence rate since the time to take the medicine correctly is critical basically?

DR. BEN-MAIMON: Can I have Slide 629, please?

What you can see here is that 73.8 percent of the women took the second pill exactly at 12 hours, but 86.1 percent took the pill within 11 and a half and 12 and a half hours.

So the reason that there was a very strict definition of exactly, and when I said 12 hours, it was exactly 12 hours. We did though, however, in order to try and make it even better, a we stated before, we bolded it in the package where it actually tells them to take it at 12 hours.

And in addition to that, we are including in the package a reminder card that will tell them not only to take it as soon as possible, but will allow them to record the first dose and record the time of the second dose in order to remind themselves that that's the time to take it.

CHAIRMAN CANTILENA: Okay. Next is Dr. Johnson.

DR. JOHNSON: I have a somewhat related question, and it has to do with how frequently people don't take the second dose at all, and so, for example, in the label comprehension study, the question seemed to get at how well they understood to take it within 12 hours, which gave away the fact that they had to take a second pill at all.

And so I'm wondering if you can give me any -- if you have any data on how many didn't take the second pill at all and if you have data on what the efficacy rate is when they only take 1.75.

DR. BEN-MAIMON: We have data from the actual use study that looks at taking the pills. As we said earlier, 92 percent took both pills. Point, two percent, one person, took only one pill. One percent, three people, took no pills. That was the three women -- it was originally, if you remember, 543 women and we were down to 540. They just didn't use the product, and we had 42 women who were lost to follow-up that we had no information on.

CHAIRMAN CANTILENA: Okay. Thank you.

Next we have Dr. Greene and then Snodgrass, Wood and Crockett.

DR. GREENE: One of the points I'd like to make with respect to this question that was just asked is there is data with respect to the efficacy of the regimen, whether it's taken 12 or even as far as 24 hours apart between the two pills, and in fact, in a randomized trial there was no difference in the contraceptive efficacy whether the pills were taken 12 or 24 hours apart. So that's just one point of information I wanted to provide.

CHAIRMAN CANTILENA: Is that information in our packet, as a reference in our packet?

DR. GREENE: I don't think so.

DR. BEN-MAIMON: I can actually show it. We have a slide.

CHAIRMAN CANTILENA: Is it from a published study?

DR. BEN-MAIMON: Sorry.

CHAIRMAN CANTILENA: Is it from a published study?

DR. GREENE: No, it's not.

DR. BEN-MAIMON: You can see here that this was 24 hours apart. This is an overall efficacy rate for all of the regimens. It is not broken out, and we don't have access to that data. We've tried to get it, but we do not have access to it. But the overall pregnancy rate was 1.7 percent.

CHAIRMAN CANTILENA: Okay. Dr. Greene, do you have another question?

DR. GREENE: The other point I just wanted to make was touched up, and that is although pregnancy can occur within five days or six days, what we're talking about is the period when the ovum is fertilizable is extremely short after ovulation so that Wilcox and others' data have indicated that an act of intercourse after 24 hours after ovulation is incredibly unlikely to result in pregnancy even without pharmacologic intervention

DR. LOCKWOOD: That's not the point. I guess the point I'm trying to make is the opposite point. If you've documented ovulation and you then show that there would be -- you've documented

ovulation. The patients had intercourse, then have intercourse again, and you show efficacy to giving the agent that second time.

It would suggest that there was a contragestive effect. From what I can discern, I don't think we have any data to suggest that that happens or any data to suggest that it doesn't happen because I don't think anybody has done that study.

That was my point.

CHAIRMAN CANTILENA: Okay. Dr. Snodgrass.

DR. GREENE: Or is ever likely to.

DR. SNODGRASS: My question is related to the issue of 1.5 milligrams once, and as I recall there was some discussion earlier about this was data that was available from outside of this country that had not yet been reviewed. I guess my question is more to the FDA.

Are there plans to review this type of data?

DR. GRIEBEL: If a sponsor submits it, then we would review it.

CHAIRMAN CANTILENA: A sponsor driven

process.

Dr. Wood.

DR. WOOD: I was going to make the same point, I think, that Mike just made, but I guess I'm concerned that we're getting into sort of bureaucratic issue where we have to demonstrate that the drug should be taken exactly 12 hours after the last dose when, in fact, in your heart I suspect that the sponsor believes that two doses taken once would be at least as effective as one dose taken 12 hours apart, and that the data that says that it has to be taken at 12 hours rather than 11.5 and 12.5, as was on your slide, just seems to me beyond the pale.

I mean, to those of us who are giving drugs to regular folks every day, they don't take their drugs 12 hours apart, and you don't make that a condition for approval of an anti-hypertensive or whatever.

So I think we've got ourselves into a bureaucratic trap where we're worrying ourselves to death about whether to take it 12 hours apart when we don't have data to support that as being an essential

part of the efficacy data.

CHAIRMAN CANTILENA: Thank you.

The trap will not actually hold the committee because we will move forward.

(Laughter.)

CHAIRMAN CANTILENA: Dr. Crockett, please.

DR. CROCKETT: Yes, thank you.

We spent quite a considerable amount of time yesterday hearing very compelling testimony about adding folic acid to contraceptives to prevent spina bifida and anencephaly in unintended pregnancies, and it strikes me during this conversation that it would be an optimal time to educate our population about the failure rate of the emergency contraception and to put a recommendation on the label that they start taking their folic acid.

Has your company considered that at all, please?

DR. BEN-MAIMON: We watched that committee meeting. No, we haven't, but we will be happy to discuss it with the FDA.

CHAIRMAN CANTILENA: At a later date.

Okay. Dr. Emerson.

DR. EMERSON: This is just a follow-up on this actual use study. Two points.

One is the idea that you excluded patients just because they asked for more information, isn't that part of actual use? I mean I go to a hardware store and ask how to use tools and still over the counter.

(Laughter.)

DR. EMERSON: And so I would think that that would be there.

And then it also seems to me that in the actual use study that what we're really interested in is how the use compares with what the people would be doing with the medical supervision, and so the point being of noncompliant patients. You know, we have that problem all the time anyway.

So I guess I haven't seen very much of this data that suggests that it's substantially worse than what compliance would be in medically supervised, prescribed medications.

DR. BEN-MAIMON: I'll answer your question

twofold. I think the issue of actual use -- and maybe the FDA can weigh in on this -- is really to try and take a population that would be using the product.

Obviously with this product it's difficult because it's such a private matter and there aren't a lot of women using it today, and so using the family planning clinics was important.

The issue here isn't though whether if women want to pursue additional information whether they can take it. The question really was if they choose not to pursue additional information, can they take it correction, and I think that's the question that the actual use study answers.

The other question is if they need additional information, can they get it, and I think that speaks to all of the discussion about the learned intermediary and the need for a learned intermediary. And it is clear that women will have a 24-hour hotline staffed by health care professionals. They will have access to a Web site, and clearly, they still have access to a pharmacist and their physician during the same hours that they normally would. It's not that

they're going to be prevented from making that contact.

And so I think your point is well taken, but because the study was designed to test whether with no information or no additional information women could use it appropriately, that's the way the study was designed.

With regard to the efficacy issues and comparing it to other trials, could I have Slide 42? And then I'll want 43 in a minute.

You will probably recall I presented this morning this slide, and this is really what this does. We basically said it's the same regimen, and it's the same dose, and given that, since we know the efficacy from the WHO study supported the safety and efficacy of the product, if women are taking it with the same pattern of use as they were taking it in this trial, it should have the same efficacy and safety profile.

And you can see that the percent of women taking it at various times is clearly similar between the two groups. That was the first pill within 72.

This is the time between the first and

second pill, and you can see again that the distribution is very, very similar with about four percent of women taking it after 16 hours and about five percent in the original trial.

So given the fact that it was safe and effective in the WHO trial the way it was taken, it should be safe and effective as an over-the-counter product.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Kweder, did you have a comment?

DR. KWEDER: No. I think that Dr. Ben-Maimon has answered it. Thanks.

CHAIRMAN CANTILENA: Okay. Actually I have a question for the sponsor.

On page 17 of your document, there was just one study that raised a statistical trend, the San Francisco study, UCSF 2000(b), which talked about a slightly lower condom use incidence. I was wondering if you can comment on that.

I think you're comparing, if I'm reading this correctly, you're comparing the pharmacy access group as compared to the clinic group; is that

correct?

DR. BEN-MAIMON: Yes, that's correct, and I think what you'll see there is that that was somewhat offset by an increase, although it was not statistically significant, in the use of oral contraceptives.

So there was no change in the overall use of contraceptives. There was a switch from the use of condoms to oral contraceptives.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Benowitz and Dr. Stanford next.

DR. BENOWITZ: We haven't heard anything about drug interactions, and we know for the usual type of contraceptives that women who are taking certain anticonvulsant drugs, rifampin, can have contraceptive failures, and one question is have you looked at the effects of enzyme inducing drugs on the kinetics or effects of Plan B, and if not, should these be a contraindication for use?

DR. BEN-MAIMON: Well, I'll make two comments with regard to that. The first is that clearly there is data on levonorgestrel, and there is

an interaction with some of these products. We have not specifically done it with this particular dose and two doses.

I think though you have to look again at the benefit-risk assessment and what you're dealing with here is the act has already occurred, and so these women are either going to get pregnant or they're not going to get pregnant, and their last chance to prevent that pregnancy is to take Plan B.

So I think you have to look at it from a safety perspective, and there is no data to suggest that any of these drug interactions present any kind of a safety concern. So even though there may be a slight reduction in the plasma concentrations or the drug may be slightly less likely to work, which is not documented, but if we presuppose that, the benefit still outweighs the risk that they take it and hope that the pregnancy is prevented.

DR. BENOWITZ: Well, just if I can follow up on that, that would be okay if there were only one possible product. If there are multiple products that have potentially different interactions and different

efficacy, I think we need to give people the rational choice about what would be the most effective.

DR. BEN-MAIMON: Right, but all of those products would have to go through the review process and their labeling would be discussed with the FDA, and then I think they would have to decide what kind of labeling needed to be put in place, but clearly this is specific for Plan B.

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: I understand, again, that the data that we have on mechanism of action for Plan B is imperfect, incomplete, but I think it's a critical issue for those women who want to understand how it works and have informed consent for use.

So along those lines I have a question from Appendix 6 from the sponsor's book. They list all of the answers to Question 7 about -- after they showed the women the package, they said, "Without looking at the label, tell me what Plan B is used for," and then classified answers as either correct and acceptable or correct but not acceptable or not correct and not acceptable, and they list them

verbatim.

And among the ones that are listed as correct and acceptable are a number of women who said that -- one of them is, for example, an abortion type thing for the day after. One was them was to kill a fertilized egg, and basically showing that some women had that understanding, and it was classified by the company as a correct and acceptable understanding of what the product is for.

And so I'm just wondering for the FDA did they also classify those particular answers as correct and acceptable for what the product is for.

CHAIRMAN CANTILENA: Dr. Lechter? Is she here?

DR. LEONARD SEGAL: Dr. Lechter unfortunately had to leave, and I don't know that I can actually specifically address how she did her calculation in her review on that particular issue. My assumption is though that she probably followed the sponsor's categorization.

CHAIRMAN CANTILENA: There were a few tables that she showed in her presentation where she

had asterisks where there was, you know, a difference between her, you know, assessment and the sponsors. But I don't recall if that specific issue was asterisked or not.

Okay. Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I think that one of the things that Dr. Stanford is getting to -- and you can tell me if I'm wrong -- is a matter of informed consent such that the patient is as fully informed as possible based on all of the information that we know about how this product works.

So I guess I would ask the sponsor first. When you've done surveys, if you have -- and you may not have this information -- in women who have taken emergency contraception and then you've asked them the question of how they perceive, first of all, the medication worked, besides one of these studies because during that time, I think when you are dealing with that immediate issue of needing emergency contraception or even within the first couple of weeks while you're waiting for that cycle to come, your perception of how it works may be different than when

you sit down and really think about it. So I think that's one point.

And then, you know, even with my background, having a lot of experience with infertility and giving a lot progesterone, et cetera, and I've reviewed the literature, there is some data out there that really does suggest at very high dosages that there may be the possibility that you're interfering with the implantation.

And so I guess my comfort level would definitely -- I would definitely be a lot more comfortable making sure that the patient or the woman who makes that decision is as informed as possible that there potentially is a possibility that still gives that woman enough information to make an informed decision and not dilute any of her rights in deciding to proceed with this medication.

CHAIRMAN CANTILENA: Okay. Doctor -- I'm sorry. You have a comment?

DR. BEN-MAIMON: We are very sensitive to the fact that there are differing views not only of how this could potentially work, but also when

pregnancy begins. And so there are actually statements in the labeling with regard to the implantation issue in order to provide women information so that they understand and that they know that this could potentially prevent implantation.

Again, we believe the data is overwhelming. We believe the medical definition, which is that pregnancy starts at implantation, is a critical point to keep in mind, but we are sensitive to the issues that others -- the opinions of others.

CHAIRMAN CANTILENA: Okay. We have Dr. Snodgrass and then Dr. Davidoff.

DR. SNODGRASS: I just wanted to follow up on the drug interaction question. It seems that if rifampin, phenytoin and others pose that potential, that this would be another argument for consideration of the higher single dose since you had lessened that possibility.

CHAIRMAN CANTILENA: Any comment from the sponsor?

DR. BEN-MAIMON: Again, the data is new. It came from the WHO study. We may very well at some

point have access to it and put an application together, but right now the application that's there is for two single doses.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes. To follow up on the mechanism question, I also wondered a bit about that because there were some data in the background packet that did suggest from ultrasound studies that ovulation may occur, but there may be what was called dysfunctional ovulation as a result of taking these pills, not that I understood exactly what ovulatory dysfunction is or does, but presumably it is the mechanism by which fertilization is impaired, but I'd be prepared to be enlightened.

But my question that I thought might help clarify the situation had to do with what is the wording on the oral contraceptives that are the progestin only, the mini pill. Because in my reading of Novak's textbook, it says, page 249 of the 2002 edition, 40 percent of those cycles are ovulatory.

So presumably there is something else going on besides prevention of ovulation in the use of

the mini pill, and I wondered what the labeling tells potential users about the mechanism.

DR. BEN-MAIMON: I would defer to the agency.

DR. DAVIS: I can read from the Plan B label, which has really been presented by the --

PARTICIPANT: What's the labeling of the mini pill?

DR. DAVIDOFF: Depo, Norplant, Micronor.

DR. DAVIS: I don't know specifically what it states on the mechanism of action. So I'm sorry. I'd have to leave a -- maybe Scott Monroe, my team leader, could comment.

DR. MONROE: I can't quote it either, but a mechanism which is likely to be operative when you're taking a continuous progestin, as we're talking about, is change in cervical mucous and affecting sperm penetration, and so forth. So that would not be a likely mechanism here, but it's considered to be a potential important mechanism with a progestin only contraceptive.

CHAIRMAN CANTILENA: Do you have a follow-

up, Dr. Davidoff?

DR. DAVIDOFF: Yes, I understand, but since I guess there is still some question about the possibility that there might be an occasional ovulation, an egg that's fertilized, is there wording in the mini pill that states something along the lines that the Plan B --

DR. BEN-MAIMON: I don't know the answer to that.

CHAIRMAN CANTILENA: We have actually Dr. Greene and then Dr. Montgomery Rice.

DR. GREENE: Just a quick point with respect to the drug interactions. Most of the drug interactions with combined estrogen-progestin oral contraceptives are really due to interference with enterohepatic circulation of the estrogen and permitting breakthrough ovulation.

That wouldn't be germane to this preparation.

CHAIRMAN CANTILENA: Okay. Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I was just going to

say I believe the packaging on the mini pill says something like "out-of-phase endometrium," along with the cervical mucous and some other stuff. So it may say something like that.

CHAIRMAN CANTILENA: Okay. Dr. Crockett.

DR. CROCKETT: Yes, this will be a short question. In your presentation this morning on one of your slides you mentioned that there were 133 pregnancies, and I was just wondering if you have the follow-up data on the outcomes of those pregnancies for us, please.

DR. BEN-MAIMON: I actually don't, except for the fact that the two or three -- I can pull up the slide. Just a second. Sixteen, please.

DR. CROCKETT: Yeah, I believe it was the one where you had your ectopic rate of two percent.

DR. BEN-MAIMON: Yeah, and that's all we have, is the ectopic rate.

CHAIRMAN CANTILENA: Yes, Dr. Lipshultz.

DR. LIPSHULTZ: Just a quick question for the sponsor. I'm interested in your data about almost a spermicidal or sperm interference of the drug in

that I know in the human a steady state of sperm ascent has been shown to be reached as early as 35 to 45 minutes after intercourse. I mean, so the data that you have on lack of sperm reaching the egg, is this inferred, scientifically shown? I mean, where did the data come from that you quote as the mechanism?

DR. BEN-MAIMON: No, there actually is a study by Dr. Kesseru -- I can never say his name correctly. Forgive me -- in healthy women where they administered levonorgestrel in these doses, and within hours afterwards they then retrieved sperm and cervical mucous from the female genital tract, and they were able to show decreased motility, changes in cervical mucous, as well as changes in pH, and it was within several hours, within 16 --

DR. LIPSHULTZ: There's already sperm in the tubes. So if there's eggs in the tubes, then there's going to be fertilization.

DR. BEN-MAIMON: Well, it's my understanding that sperm generally resides in the lower female genital tract and then migrates up in

waves, which is why the sperm are sort of waiting for the egg for ovulation, and why it's actually the days leading up to ovulation where women are most fertile.

I defer to the experts on the panel who know this physiology probably much better than I do.

CHAIRMAN CANTILENA: Okay. Since there are no takers for a lecture --

(Laughter.)

CHAIRMAN CANTILENA: -- are there any general questions for clarification, other than what's already been asked about the actual use study and the comprehension study?

Dr. Crockett.

DR. CROCKETT: In our discussion we talked a little bit about the menorrhagia that happens, especially if women use this medication more than one time during a month, and as a practicing OB-GYN, I already see a ton of bleeding disorders, and I'm not anxious to see a whole lot of patients coming in with this.

So I was wondering if you have any estimate on the number of office visits that this is

going to generate from irregular bleeding or the public health impact on that.

DR. BEN-MAIMON: No, I don't have data. What we do know is that -- and I'll show this -- that this is with repeat use, and this is from the women who are using it for postcoitus, and you can see that intermenstrual bleeding occurs in about 40 percent of women. Again, if they only use it once during the cycle, it is gone, and then they get back on their regular cycle, but you can see there's a whole host of bleeding disorders when used initially.

Most women have their period on time. It can be slightly earlier or slightly later. Clearly if they miss a period, there is a recommendation on the label that they do a pregnancy test and follow up with their physician, and so again, if used once within the cycle, then bleeding irregularities should be minimal.

One other point. You asked about the follow-up of those pregnancies. The only point I can make is there were no serious adverse events reported in that trial associated, and clearly congenital anomalies, those kinds of things, abortions or

requirements for hospitalization would have been counted. So that does speak to that a little bit.

CHAIRMAN CANTILENA: Yes, Dr. Hager.

DR. HAGER: Could we put to rest the question that we've danced around since this morning? And that is the long-term effects. We've touched on it; we've gone away from it. We're told that it would be answered this afternoon, but just some information that you would have for us on long-term effects with either single use or multiple use.

CHAIRMAN CANTILENA: I think actually you heard some information from the FDA. Dr. Davis had some information from the literature and from other, you know, drugs.

You know, in addition to that or, you know, on that?

DR. HAGER: I didn't feel that that was the final word. Is that it?

DR. GRIEBEL: That's what we have. I don't know if the sponsor has anything they'd like to add, any details.

DR. BEN-MAIMON: No, I think Dr. Davis

made a very nice point. Levonorgestrel has been on the market for a very long time in continuous use pills. There's data on very high doses, given repeatedly, and I don't know what more we could propose or show.

CHAIRMAN CANTILENA: Okay. Dr. Hager any other point on that?

Okay. Are there any questions from the committee regarding the label comprehension and actual use study?

And I guess I would ask the sponsor how it was that you ended up with basically a study that was done in family health, you know, centers and you had such a small number of, you know, pharmacies.

DR. BEN-MAIMON: From the actual use study you're referring to?

CHAIRMAN CANTILENA: Yes, yes, from the actual use study.

DR. BEN-MAIMON: The reason was that this is a very difficult product to evaluate. Obviously you can't go advertising for women who have had unprotected sex to please come, you know, to a

counter. And so there was discussion with the FDA -- sorry. I didn't mean it to be funny.

After discussions with the FDA, clearly, it was decided that we would try our best to simulate an over-the-counter environment.

The one thing I would want to point out is, you know, when you look at it in contrast to a prescription environment, we actually, I think, did very closely simulate the over-the-counter environment. The woman had to determine that she needed something, that she had had unprotected sex and she had an event that needed intervention.

She then had to be motivated to go and seek help at a family planning clinic. She walked in and she either said, "I've had unprotected sex," or, "I need emergency contraception," one of the two, and she was given no further information except to be told that there was a study and did she want to participate.

If she said yes, she was then given the package, and she determined whether or not taking Plan B was appropriate. If she did not think that it was

appropriate, she was not enrolled. If she did think it was appropriate, she then signed an informed consent. She was given the cards, and she went home.

So in answer to your question, this was the best we felt that we could do in order to make sure that we could perform the study in a timely fashion and have adequate numbers of women to be able to give some sort of clear indication as to whether or not they could take the product appropriately and take it correctly according to the label.

CHAIRMAN CANTILENA: All right, but what she was given actually was the -- I assume she was given a copy of the informed consent document. Is that true?

DR. BEN-MAIMON: No, she was just given --

CHAIRMAN CANTILENA: Just she signed it and that was it?

DR. BEN-MAIMON: She signed it, and that was it.

CHAIRMAN CANTILENA: Okay, and I guess the only other, you know, concern I have is because it was such a short study and you go through the process of

sort of enrollment and informed consent, and then the whole study was only for one month; are there, you know, concerns that you have that are different from those we heard from FDA with regarding the generalizability of that short study into the long-term environment of, you know, over the counter?

DR. BEN-MAIMON: Well, again, I think that the issue here is whether or not women could take it without contraindications and whether they could take it correctly. And since this product is taken, you know, two doses 12 hours apart, that was able to be assessed.

The need for a longer study would have had to have been done if we were looking at pregnancy as the primary outcome, and here because it's the same regimen and the same dose as the already approved prescription product, we were able to, I think, make the determination that it should be as safe and effective as the prescription product as long as it was taken in a similar fashion, and so that's how I think you can deal with that.

CHAIRMAN CANTILENA: Okay. I don't think

there are any -- actually, Dr. Patten has a question.

DR. PATTEN: Yes.

CHAIRMAN CANTILENA: Patten and then Montgomery Rice.

DR. PATTEN: A question or comment coming from the label comprehension study. I note that one of the conclusions that was well understood was that the first pill should be taken within three days, and a concept less well understood was that the first pill should be taken as soon as possible after unprotected sex.

And so when I look at that information on the label, I see that's a fairly complex sentence, and I'm wondering if that isn't what is contributing. I mean, the most important thing is that the woman understand that she take it as soon as possible after unprotected sex.

So I would just suggest that you break that sentence into two sentences or in some way figure out how to simplify it so that the confusion goes away.

DR. BEN-MAIMON: We'll take that into

consideration. Thank you.

CHAIRMAN CANTILENA: Yes, Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I don't know if you were alluding to this, but you know, when we give a prescription to a patient for emergency contraception, we don't necessarily see that patient back in a week or two in our office. You know, we tell her if she has a cycle, then she's fine and she doesn't have to come back, and then you would see that patient for a routine visit.

And so, I mean, people who prescribe emergency contraception have probably a lot of experience or a fair number of patients who they have given this and haven't seen any long-term issues with that or problems with follow-up because generally the information, you tell them that you should have your cycle. If you don't have your cycle in a couple of weeks, then you will see them back under those circumstances.

CHAIRMAN CANTILENA: Excuse me. I guess my point was that's the environment where you're

involved. You're educating the patient, and I was just sort of trying to get a handle on what the extrapolation would be to a setting where, you know, there is not that individual there, and that information will now be, you know, provided through the outside, well, you know, through the insert and through this program.

So I was just trying to get a comfort level with the extrapolation of how it's currently used and the extensive experience in that setting to how it will apply to the OTC setting, as outlined.

Go ahead.

DR. TRUSSELL: Probably the most reassuring part of the actual use study is that the 40 percent of people who had had a prior encounter with a learned intermediary to get emergency contraception did not use it any better than the rest of the people who were naive users.

(Laughter.)

DR. TRUSSELL: So if there is a terrific benefit to seeing the learned intermediary, it doesn't last very long.

(Laughter.)

CHAIRMAN CANTILENA: Not to defend the learned intermediary, but our committee over many years has heard that one of the reasons it should be over the counter, X, Y or Z should be over the counter was because, you know, the regular system is not very good, and I guess I would, you know, not like to hold that up as a reason for approval for over the counter, because the other system is not very good.

Dr. Uden.

DR. UDEN: During the public hearing, we heard from a woman who represented the Latina population, and you did all of your label comprehension studies with English speaking, English reading individuals. What information do you have that this was done in Spanish for the Latina population, that the same words would be appropriate for that culture, and what would you propose for Spanish labeling?

DR. BEN-MAIMON: Well, first, let me show you that there was a percentage, about 14 percent, which does mirror the U.S. population for the actual

use, and 23 percent of Hispanics in the label comprehension. So we did have a sample that mirrors the general population.

Also, I think the low literacy group may have been low literacy, some of those women, because of the difficulty they had speaking English, not necessarily because they were uneducated necessarily.

But I think you're touching on a very important point, and we have talked internally about whether or not we should have the label in Spanish, and we will discuss that with the agency.

DR. UDEN: Or a number of other languages.

DR. BEN-MAIMON: Yes.

CHAIRMAN CANTILENA: Okay. Thank you.

I think unless there are any other questions that need to be clarified -- I'm sorry? Okay, yes. Dr. Berenson.

DR. BERENSON: I have two questions. The first one was in the actual use study -- actually I think it was a labeling study -- there was at the beginning a portion where the woman was allowed to look at the package and then the package was taken

away from her and she had to answer some questions, and I was curious as to why that was done because in actual practice I don't know why anyone would ever take the package away from her and then quiz her about it.

(Laughter.)

DR. BERENSON: It would seem more actual use if she could have continued to look at the package.

The second thing was in the packaging that was sent around the room, I don't know if that's the proposed packaging for marketing, but there were no instructions on the outside of the box where many over-the-counter medications do have instructions on the outside of the box, and it could clearly state there things like "take as soon as possible" and within 72 hours.

DR. BEN-MAIMON: It is on the box.

DR. BERENSON: I withdraw the second question.

DR. BEN-MAIMON: That's just the way the study was designed. It may have been better, but the

idea was really it was only one question that was asked initially, which was what is it for. It was an open ended question, and that's just the way the study was designed, but your point is well taken.

CHAIRMAN CANTILENA: Okay. Dr. Wood.

DR. WOOD: I want to return to the issue about the as soon as possible. It seems to me based on the literature review that we had, the drug will be taken in potentially one of two ways. It will be taken by people who seek it out to use as an emergency contraceptive after an event and by others who keep the drug in their bathroom cabinet to use appropriately.

That being the case, it would seem to me that the statement "as soon as possible" and "within 72 hours" should be separated because for these individuals they would use it differently. For somebody who already has the drug, they should use it as soon as possible. For somebody who has to go and seek it, they should still use it as soon as possible, but certainly within 72 hours.

And it seems to me that distinction needs

to be made in the label more clearly.

DR. BEN-MAIMON: Okay.

CHAIRMAN CANTILENA: Okay. A final question, Dr. Crockett.

DR. CROCKETT: This is a question to our over-the-counter committee members. I wondered regarding other medications proposed for over-the-counter use how you consider the illiterate population and what impact it would have on them.

CHAIRMAN CANTILENA: Yes. Other sponsors, I mean, I'll try to answer it, and then, Curt, hop in, please, but other sponsors with general products have included, you know, pictograms and things on the label which were, you know, tested and, I think, have been shown to be helpful, and I can't remember the products offhand. Perhaps Dr. Ganley or Dr. Rosebraugh would have some specific examples of what products.

So they've shown some efficacy in terms of, you know, labeling, you know, with that tool. Any other comments, Curt?

DR. ROSEBRAUGH: No, not really. The only distinction I would add is that when we do pictograms,

it's usually on the package insert. You really can't have it in the drug facts. That's part of the regulation.

CHAIRMAN CANTILENA: Okay. Well, why don't we, instead of waiting until 3:30 for our break, why don't we take a 15-minute break at this point, and then we'll come back and get into the questions?

(Whereupon, the foregoing matter went off the record at 3:13 p.m. and went back on the record at 3:32 p.m.)

CHAIRMAN CANTILENA: Will the committee please take their seats?

A couple of individuals on the committee have asked just for an opportunity for probably one or two more clarifying questions about the CARE Program. I think the first person was Dr. Benowitz.

DR. BENOWITZ: One thing that was striking this morning was despite the enormous public health importance of emergency contraception and the enormous amount of money spent in the State of California to try to get people to know about it and use it, that it was used so little and so few pharmacies used it and

so few physicians promoted it.

And my question is: with the experience in California, why or how do you plan to do better?

DR. BEN-MAIMON: It's an important question, and we actually think that it's a combination of issues and they both have to occur simultaneously, and that is we need to educate consumers, but we also need to educate physicians as well as pharmacists, and then we also need to educate and we also need to make it available so that when people go get it, when they try to get it, it's there.

And it's sort of the chicken or the egg. People don't carry it because it's low volume. People don't go get it because they get frustrated, as we heard from many docs who called prescriptions in.

And so I think what we're talking about here is first using three mechanisms to get to consumers. The first is we have a sales force because we are actually -- we sell proprietary drugs and a lot of oral contraceptives. We have a sales force of 250 sales reps. that visit about 30,000 doctors across the country.

And so we will be using that as a mechanism to distribute educational materials with the intent hopefully that when a woman walks into the office there will either be a display or a receptionist will say, you know, "Here's some materials we'd like you to read while you're waiting," which may be a way to outreach in a way that we already see these doctors.

Then of course, there's radio and advertorials that, like we said, are public service in nature, that really provide information and encourage discourse either to call the hotline or to look at the Web site so that women become more educated and more aware.

I think also there is somewhat of a word of mouth issue. You know, the more women that become aware of it, the more likely that other women will become aware of it because they talk to each other.

And then finally, from the standpoint of stocking, we will be working with the drug stores to make sure that they carry the product. We have very good relationships with retail pharmacies and chain

drugstores to make sure that it is available when women try and seek it out.

CHAIRMAN CANTILENA: Is that all right, Neal?

Okay. Are there any other questions? Dr. Blaschke.

DR. BLASCHKE: Well, just as a follow-up to the question about the CARE Program, one thing that I'm interested in is your monitoring program. You described it in a little bit of detail in the briefing book, but I wonder if you could add how you expect you might use the information you get back during the monitoring program to modify, for example, the label, which seems to me to be something that people are concerned about that could be improved.

DR. BEN-MAIMON: Well, I think, first of all, we were planning on doing survey type questions, and then obviously using publicly available information like CDC data, and the issue really is that I think this would be a hard population to survey the patients themselves.

But we have lots of contacts, as we've

said, with physicians. Through surveys and questionnaires, we hope we will be able to determine what kinds of questions are actually being asked, where people are having trouble, where they're having concerns, where they're having to contact the pharmacist or the health care provider.

In addition, the data from our hotline itself can be pursued in order to find out what questions are actually being asked on the hotline and then clearly to follow that up with discussions with the agency for labeling modifications.

CHAIRMAN CANTILENA: Okay. Thank you.

Why don't we now go to the questions for the committee? And the format that we'll use here, as I said earlier, we'll actually go around the entire table and have you vote and then state your reasons for your vote because I think that will be very helpful to the FDA to hear sort of your thoughts behind your vote.

And I think actually just before we do, I would like to ask Dr. Alfano if he has any comments. There are 29 individuals at the table, but 28 voters.

So are there any comments that you'd like to make, Dr. Alfano, before we head into the vote?

DR. ALFANO: No.

CHAIRMAN CANTILENA: Okay, all right. And we're only going to make one sort of addition to the first question. The first question: does the actual use study demonstrate that consumers used the product as recommended in the proposed labeling?

And as you answer that, I also would appreciate your stating what improvements could be made, in your opinion, to the label as it's out there now.

So why don't we start on this side of the table, Dr. Hager, answering Question 1 and stating your reasons and then talking about the label?

DR. HAGER: My answer is yes. The data indicate that depending on how you evaluate it, between 13 and 28 percent of the individuals incorrectly used the drug, although that did not prove to be deleterious in a large number of cases.

Regarding inclusions with the labeling, I personally would hope that undiagnosed bleeding would

be reincluded from a gynecologist perspective. It can be a symptom of ectopic pregnancy. It can be a symptom of other gynecologic conditions that would warrant investigation.

The potential effect, the mechanism of action on the endometrium, I believe, should be included so that the patient has adequate informed consent as to the potential that it may alter implantation.

And finally, a strong emphasis, an underlined emphasis that abdominal pain is an indication to seek medical care immediately because of the risk of ectopic pregnancy.

CHAIRMAN CANTILENA: Okay. Thank you. There's a comment over here from FDA.

DR. ROSEBRAUGH: I just wanted to make a point of clarification. Since mechanism of action has come up several times, the way the sponsor is proposing it right now, as I understand it, the mechanism of action will be on their package insert. So it would not be at the point of purchase, and it would be helpful if people would give us their

thoughts about that.

Let me just explain point of purchase real quick. I'm sorry. That just means that when they pick it up, they can't see it until after the buy it and open it up.

DR. HAGER: Yes, my feeling is that it does need to be available to the consumer at the point of purchase. The conflicting information that Plan B does not cause abortion and yet the inclusion that it does have an effect, a potential effect, on the endometrium, I think, is contradictory, and I would like to see a very plain statement that is at the point of purchase so that the consumer can make an informed decision as to whether or not they want to take this with the potential that it may affect the endometrium and implantation.

CHAIRMAN CANTILENA: Thank you.

Dr. Lam.

DR. LAM: I would say yes to the question that the actual use study demonstrates that the consumer used the product as recommended in the proposed labeling, and I actually think that the label

is better than some of the other labels that have come before the OTC committee in the other study.

And actually, I am satisfied with the sponsor in terms of trying to improve the adherence rate by putting the little labels indication for the user to write down the time in order to remind them when you would be the appropriate time to actually take the second dose or something.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Lipshultz.

DR. LIPSHULTZ: Yeah, I also agree that it does demonstrate as stated.

I would also say that in the labeling I would like to see likewise on the immediate packaging some more information for the consumer about mechanism of action and also somehow clarify the sentence about as soon as possible, as well as the statement "within 72 hours" so that it is better understood.

CHAIRMAN CANTILENA: Thank you.

Dr. Johnson.

DR. JOHNSON: I feel that the appropriate use was documented in the actual use study. In terms

of improvements to the label, I think one of the problems with over-the-counter labels is we always want more information on them than is possible in the physical space that's available.

And so while I think in a perfect world it would be perhaps nice to have the mechanism on the outside, it's probably going to be at the expense of some other information that's already on here or they're going to have to have a very large box.

And so I don't feel strong. I think it's important that it's in the package insert. I don't feel strongly that that's available on the outer carton.

CHAIRMAN CANTILENA: Okay. Dr. Macones.

DR. MACONES: Yes, I think the answer to this question for me is yes, that the actual use study did demonstrate that users can be use this product well.

In terms of the label, just a couple of points already mentioned. I would favor adding something about the mechanism of action onto the box itself so that people can look at it in the store and

understand how it works. I think that would be very important to some people about whether or not they would choose this.

And I also think I agree with Dr. Hager that I think there needs to be some more clarification within the box about why abdominal pain is an important side effect for people to know about and to notify their physicians.

CHAIRMAN CANTILENA: Thank you.

Dr. Patten.

DR. PATTEN: I would say yes to the question, and my concerns with the label, I've already stated one of them. I think the sentence having to do with when this product should be used is too confusing, and I would also suggest that a way be found to really emphasize to users how important it is to take it within the first 24 hours after unprotected sex because beyond that, as we saw in the slide, its efficacy diminishes.

So I'm not sure. I leave it to the experts to discover what that way would be, but I think it would be very good to express that to women

so they really understand the urgency about using it right now.

Also I just would raise a question about the front of the box, Plan B emergency contraception. I just raise the question should there be added there the statement that this is for use after unprotected sex. "Emergency contraception" can have different meanings to different people. I'm out of birth control pills, you know. Should I buy this or should I buy a package of condoms, et cetera?

CHAIRMAN CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: I say yes also to the actual use study showing the product's capability of performing the task. The concern that I have is, I guess, twofold. One is to translate the 7,000, 8,000 individuals who have taken the product into the eight to ten million individuals who are going to be available to use these products, and the second thing is to make sure that those individuals understand what the product is to do.

And secondly, to worry about the potential

difficulty, the barrier of, I guess, the amount of cost of the product for a lot of our underserved individuals in my community, and I think my individuals, like the community that you talked about in your drugstores, they have some barriers of getting to the product, and therefore, I don't think these products will be on the general shelf in my particular neighborhood either, but that's one of my concerns.

CHAIRMAN CANTILENA: Thank you.

Dr. Crockett?

DR. CROCKETT: I'm going to say no. I don't think the actual use study demonstrates that consumers used the product as recommended in the proposed labeling. I think it showed that they can use it with the proposed labeling in the setting of having access to education and accountability afterwards, and I think those are important factors to consider in bringing a product like this from behind the counter to over the counter.

In regard to the labeling, I would like to suggest that there be stronger emphasis on putting the failure rates for the 24 hour, 48 hour, and 72 hour

first pill taking into the product labeling so that patients more clearly understand the risks and the pregnancy risks from delaying use of it.

And also, I'm going to reiterate that I think if we're going to go that far, that we should also put in a statement about needing to take folic acid in case that there's an intended pregnancy.

CHAIRMAN CANTILENA: Dr. Uden.

DR. UDEN: Yes, and I won't say any more. I'll pass my time along.

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: I think, yes, it does demonstrate it for short-term use, short-term study.

In terms of the label, let me just make the suggestion of something along the lines of Plan B may work to prevent pregnancy by preventing fertilization or preventing implantation. Plan B does not interrupt pregnancy after implantation.

I think the "after implantation" is important because some women would understand abortion to mean if it says it does not cause abortion, they would understand that to mean after fertilization, and

I think the language needs to be unambiguous for people at different points of understanding.

I also, since we are talking about the label, have one other comment on the label, and that is how well does Plan B work. I think the estimate given there is not the most accurate estimate that could be available. My proposed wording would be something like Plan B lowers the risk of pregnancy about 84 percent when used as soon as possible within 72 hours and no further intercourse occurs during the menstrual cycle. In typical use, it is about 72 percent effective.

Now, those percentages are not the point. The percentages could be changed depending on the study, but the 89 percent that's quoted is a perfect use quote, and I note that in the package insert later when they're talking about all of the other contraceptive methods, they quote typical use for every other method, and they're only quoting perfect use here.

I think it's important to quote both perfect and typical use if you're going to quote

effectiveness, and it's also important to use the best available estimates of effectiveness, which I don't think we currently have in the 1998 analysis.

And there are other experts in this panel, such as Dr. Trussell, who have done more updated estimates for Yuzpe, and they seem updates with a more reasonable methodology could be done for Plan B relatively easy by getting the data and reanalyzing them.

And I'm suggesting that that should be what's on here, not the 89 percent.

CHAIRMAN CANTILENA: Thank you.

Dr. Benowitz.

DR. BENOWITZ: I would say yes to the question, but I would also say that I think the goal was not met in that only 37 percent used it within the actual use study within 24 hours, and so I would go along with the previous panel members in saying that the instructions should be stronger, and maybe some quantitative data should be provided about how important it is to use within 24 hours, not to wait for 72 hours. I think that is really key.

With respect to mechanisms of action, I'm sympathetic with the idea of doing it. I'm concerned that technical language like that on the outside of a package will not do very much. Most people won't understand the suggested language that we've heard so far, and I'm concerned that you can't do justice to the issue on the outside of the package; that the package insert may be the only place you can explain it.

CHAIRMAN CANTILENA: Dr. Lockwood.

DR. LOCKWOOD: Yes to the question. I would actually eliminate the line "if breast feeding, ask the doctor before use." That will give you the only person advocating any elimination of words. That would be good.

And I agree wholeheartedly with the emphasis about ectopics. In this internal blue mini insert, whatever it's called, I would emphasize that all in bold rather than just see a doctor right away if you have stomach pain. I think it's critical that they have a sense that they link the possibility of an ectopic pregnancy with the pain and notify the doctor.

I would also recommend the language on mechanisms be put in this internal insert rather than the external one for the same reasons. It would be impossible to describe it.

But I would eliminate in the first little page of this insert where it says "pregnant women (in Plan B cannot cause an abortion)," I would just eliminate "Plan B cannot causae an abortion." I think rather than get into the semantics and the arguments about what an abortion is, I would just eliminate that phrase, and somewhere in this little insert, I would explain that the mechanism of action may be the prevention of fertilization. I think most people know what fertilization is, and then some lay language that refers to "or implantation."

CHAIRMAN CANTILENA: Thank you.

Dr. Tulman.

DR. TULMAN: I would vote yes for the first question, and I also have some suggestions for the labeling. I think the mechanism of action is better served in a package insert. I think you would get to a point that the font would become unreadable

on the outside of the box unless we have a huge box.

I do think it needs to be emphasized, however, under directions. I think "as soon as possible" is a rather casual phrase. I think why not the word "immediately"? I think it's more precise.

Also, I think if there's any directions that come with this, and I don't recall whether the sponsor said anything about whether or not on a full stomach, on an empty stomach, with water, with whatever, if there's any other types of restrictions or if you can take it, indeed, full, with food, without food, juice, water or whatever. I think that should be on there.

And also the other question I had on here concerns stomach pain, and you didn't mention whether that was gastric pain or cramping or what the precise nature of the pain was.

(Participant speaking from an unmicked location.)

DR. TULMAN: Yeah, because that's kind of an imprecise. You know, is it like pain like from indigestion or is uterine cramping pain? And I think

you could be more precise about that.

That's all.

CHAIRMAN CANTILENA: Okay. Dr. Trussell.

DR. TRUSSELL: My answer would be yes to the first question, and the most important change that could be made to the label is take both pills as soon as possible.

CHAIRMAN CANTILENA: Which, of course, is not the way the application has been filed.

(Laughter.)

CHAIRMAN CANTILENA: So you're voting to reject the application; is that correct?

(Laughter.)

CHAIRMAN CANTILENA: Okay. Dr. Giudice.

DR. GIUDICE: I say yes to the question and I have the following recommendations for the label.

First of all, I agree with Dr. Hager with reinstating undiagnosed vaginal bleeding for the reasons stated and agree with the previous comments on abdominal pain, seeking immediate care of a physician, and clarifying whether this is stomach, abdominal or

pelvic.

Of concern in the label comprehension study was in the low literacy group that the objective for backup, not regular contraception, was only 46 percent. So I would bold and cap the word "backup" under "Plan B is a backup contraceptive."

In addition, even though transmission of sexually transmitted diseases was well comprehended, I still would bold and cap "Plan B does not prevent HIV," again to essentially send the subliminal message that barrier contraception should be continued.

Thank you.

CHAIRMAN CANTILENA: Okay. Thank you.

I vote yes, and in terms of the label, I think perhaps something that's not been suggested in terms of the possible mechanism of action could be that the FDA in the advertising and the information sheets that are sent out to physicians' offices and/or pharmacies, they be required to have possible mechanisms of action there.

With regard to the item on the outside, which says Plan B is not recommended for, you know,

regular contraception, I think something strong like "is not FDA approved for that" could help, you know, enforce that.

And I would agree with the comments about stating the information about vaginal bleeding as well.

Dr. Tinetti.

DR. TINETTI: I vote yes, and for the labeling, my only concern is we're adding too much, and it's well known that the more we add to the labeling, the less message people get across. I think the key message as I hear it, again, "as soon as possible." So that clear the wording that is; number one, that this is only for after unprotected intercourse, and number three, that it's not a protection again sexually transmitted diseases I think are the three most important messages that need to be on the label.

CHAIRMAN CANTILENA: Dr. Hewitt.

DR. HEWITT: I vote yes to the question. I think it has been clearly demonstrated that the majority of patients are able to use the medication

appropriately.

My only comments about the current packaging would be I agree with the statement of removing the issue related to breast feeding. I agree with the importance of emphasizing to take the medication as soon as possible, and I think a statement educating patients that the sooner they take it the more effective it is may be important to include somehow.

And I agree with removing the warning about the abnormal vaginal bleeding. I think from caring for patients as a gynecologist, there is such a broad interpretation of abnormal bleeding. Patients where their period lasts six days instead of four days that month might interpret that as abnormal bleeding. Some mid-cycle ovulatory bleeding might be interpreted as abnormal.

And then young, healthy, reproductive age women with the majority of the diagnoses associated with abnormal bleeding, I can't imagine how taking one course of Plan B would negatively impact their health, and I think that that might preclude patients from

taking it that otherwise would benefit from it.

CHAIRMAN CANTILENA: Dr. Greene.

DR. GREENE: I would respond yes to the question, and the point that you made is the one that I was just going to make, that although abnormal bleeding or undiagnosed bleeding could be a problem, it's hard for me to imagine any problem that would preclude the use of this medication or that this medication would exacerbate.

So I believe that it should also be eliminated from the contraindications to use.

I would like to point out one obvious thing with respect to the abdominal pain issue, and that is that if you look through the actual use data, about 14 percent of patients reported abdominal pain and another 14 percent reported nausea and vomiting.

Let me just point out the obvious, that if somebody has an ectopic gestation, it's going to be four weeks; as the result of failure of this medication to prevent pregnancy, it's going to be four weeks after she has taken the medication, not 48 hours later.

So rather than trying to distinguish whether the abdominal pain is cramping up or lower pelvic, we could just simply alert her that if she has pain weeks after use of this medication, that it might be an ectopic gestation, not within 24 to 48 hours of use of the medication.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: The answer to the question is yes. I think the actual use study did demonstrate the appropriate use.

But I do note that the patients were in all of the circumstances studied pretty much self-directed. I'm interested in the patient who has not heard of emergency contraception, who wanders into the pharmacy and is looking for a solution to a problem.

For that reason I'm going to encourage the pharmaceutical company to think of defining "emergency contraceptive" in layman's terms on the outside of the package because perhaps people don't pick it up, turn it around and get a good conception -- conception?

(Laughter.)

DR. CLAPP: -- understanding of the use of

the medication.

So I'm encouraging the consideration of putting on the outside what you say on the back of the package. Emergency contraception for use in case of birth control failure or unprotected sex in small print underneath.

Secondly, the mechanism of action I think best belongs on the inside of the package. The package is a lot to digest on its own, but would become very cumbersome with that information on the outside.

But giving patients the opportunity who want to think about it briefly because they should think about it quick, within 24 hours preferably, perhaps a Web site or a phone number could be included on the outside of the package to direct them if they have questions before they purchase it.

But I think that the important consideration to using the medication promptly can't be understated. I'm concerned that the mention of 72 hours gives people perhaps the thought that they have an option of waiting until 72 hours to initiate the

treatment, giving them a false sense of security.

And in people who are financially pressed, it could be, "Well, let me wait another day and see if I can borrow the money," or see that 48 hours has passed and then you just get there at 71 hours and start taking your medication.

We perhaps have given them a false sense of security or comfort with that. So I'm encouraging clarity with the "as soon as possible" and with emphasis within 24 hours but up till 72 hours so that there is a sense of urgency associated with it.

And as far as the other two issues, I think vaginal bleeding certainly Dr. Hewitt said it very perfectly. I think it should be removed.

And breast feeding, there's no necessity to include it on the package.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: The answer to the question would be yes, and my additions to the label would be many of what have already been stated regarding mechanism of action in the package insert, for example; 24-hour use period or as soon as possible;

and the elimination of the breast feeding statement. I think those are all important considerations.

Another point that is not directly to the label per se at this point would be consideration down the road post marketing of a label comprehension study in those who are less than 18 years of age.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: I also vote yes for the actual use study demonstrating that consumers use the product as recommended. I agree with the comments about putting the mechanism of action inside the package because I think it's a little complicated for the front of the box.

I also think removing the statement about vaginal bleeding is fine. As far as having menstrual changes there, you might want to qualify that as short-term menstrual changes, and again, to emphasize the timing perhaps with an additional statement that the drug is most effective if used within 24 hours.

And I also agree with bolding that this is a back-up method of contraception.

CHAIRMAN CANTILENA: Dr. Blaschke.

DR. BLASCHKE: Yes. I also vote yes on the question, and the two things that I would emphasize is I do believe that the front of the package probably could be improved to indicate that this is a post intercourse method of contraception just to eliminate that problem.

And I agree with what's been said by a number of others about emphasizing the importance of early use with data or in some mechanism.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: I also vote yes. I would caution, however, against studding the outside of the packet like a Christmas tree with all sorts of issues. I'm particularly concerned about putting things on the outside of the package which are unsupported by data.

I haven't seen any data today to suggest that ectopic pregnancy is more common with this drug than with other forms of contraception. It's not on the package for other forms of contraception, and in fact, the data that we saw presented didn't suggest that it was more common than it was with any other or with no contraception.

So the idea that we just sort of say that beware of abdominal pain seems to me to make relatively little sense.

Similarly with vaginal bleeding, and we don't suggest that aspirin has a treatise on prostaglandin synthase on the outside of the packet, and I would be against putting the mechanism of action for this drug on the outside of the packet for the same reasons that I would not suggest that we start legislating for acetaminophen or aspirin or any other complex mechanism of action, particularly when it's so speculative.

CHAIRMAN CANTILENA: Dr. Berenson or -- excuse me -- Dr. Emerson.

DR. EMERSON: My answer would be yes. I agree with the desirability of having quantitative data about the waning of the effect with time since unprotected sex.

I also agree with the idea of putting the mechanism of action inside rather than complicating the box.

And then the other question that I do have

is if there is any time period at which you shouldn't use this twice, I would think certainly 12 hours, unprotected sex twice within 12 hours would be certainly one limit, but if there is any sort of a limit, I would think that that should be included, that you know, either through the idea that efficacy persists for 48 hours, that there would not be a need to repeat this within 48 hours or if it posed problems medically for repeating this within 48 hours or whatever, I think that some sort of limit should be placed.

CHAIRMAN CANTILENA: Dr. Berenson.

DR. BERENSON: I would vote yes to the first question, and regarding the package labeling, I would suggest that less information rather than more be included on the outside of the package.

Personally I'm at an age where I'm developing presbyopia. So I guess that makes me not a great candidate to need to use Plan B.

(Laughter.)

DR. BERENSON: But the type is quite small on the back. While that is normal for many packages

that are sold over the counter, in this particular case the need for the patient to be able to read the directions for use, I think, and use it correctly is stronger due to the adverse effects that could result.

So some particular recommendations I have how to get the print larger is to, first and foremost, remove the statement of breast feeding as has been stated before; ask a doctor before use. I'm not even certain why that statement is on there because, as physicians, we would just give the Plan B anyway to a breast feeding patient because a great many patients each year get pregnant while they're breast feeding. So that certainly is no protection.

Second, I'm not sure why every side effect, every possible side effect is listed on the back of the package. It seems to me that could also be in the package insert.

Third, I don't know why the active ingredients have to be listed on the front of the page and the back of the box.

So there seem to be several opportunities that they could get things off and make the print

larger.

Finally, for the same reasons, I would agree that the mechanism of action should be in the package insert rather trying to put one more additional thing on the outside of the box.

CHAIRMAN CANTILENA: Thank you.

Dr. Davidoff.

DR. DAVIDOFF: Yes on the question, and I'd also weigh in on the issue of the wording about timing because I think it's not just a question of urgency, but specificity. And I think the data do support specifically, as a number of people have pointed out, the rapidly decreasing efficacy over time.

So I would urge not to wordsmith here, but something along the lines of putting a specific indication of earliness. "As soon as possible" is much too vague.

CHAIRMAN CANTILENA: Thank you.

Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I would keep in vaginal bleeding, but I would definitely move it to

the warning section instead of the side effect section, which it is now, and I would call it unexpected vaginal bleeding because the patient should expect to bleed at a normal time or so on the next cycle because I do think that is one of the indications of possible ectopic.

And so if it's in a warning, the patient may have some better information instead of a side effect because it's more of a warning. And I think the mechanism goes on the inside of the package insert, and my answer is yes.

CHAIRMAN CANTILENA: How did you know we were going to ask that?

DR. MONTGOMERY RICE: I could tell by the look on her face she was getting anxious.

CHAIRMAN CANTILENA: Okay. Well, since you're on a roll, then why don't we continue with that side of the table -- oh, I'm sorry. I have to read the tallies.

We had 28 voting, 27 yes, one no, zero abstain.

Okay. Question 2, and we'll start with

this side of the room, Dr. Montgomery Rice. Question 2, and we'll start with this side of the room, Dr. Montgomery Rice, Question No. 2 states: are the actual use study data generalizable to the overall population of potential non-Rx users of Plan B?

And here it's a yes or no with your reasons. Thank you.

DR. MONTGOMERY RICE: I do think if you review the data from the study that these are the people who would come in for emergency contraceptive, but clearly, they had to know that emergency contraception existed. And so I think with the appropriate marketing, other people would be more educated and would know that it potentially exists.

So I would say, yes, the data is generalizable to the overall population.

DR. DAVIDOFF: I would also say yes to the question. Sampling is always a difficult challenge, and no sampling is perfect unless you sample the universe, but I think it's a reasonable approximation.

CHAIRMAN CANTILENA: Okay. Dr. Berenson.

DR. BERENSON: Yes, I think it was

generalizable.

CHAIRMAN CANTILENA: Dr. Emerson.

DR. EMERSON: Statistics means never having to say you're certain. I would say, yes, it's acceptably generalizable.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Yes.

CHAIRMAN CANTILENA: Yes. Dr. Blaschke.

DR. BLASCHKE: Yes.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: Yes, but I think it really should be translated at least into Spanish and possibly into other languages because it was only done in people who speak English well enough to participate in the study.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: The answer is yes, and that would, again, be based on the data that's presented.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: Yes.

CHAIRMAN CANTILENA: Dr. Greene.

DR. GREENE: Yes.

CHAIRMAN CANTILENA: Dr. Hewitt.

DR. HEWITT: Yes.

CHAIRMAN CANTILENA: Dr. Tinetti.

DR. TINETTI: Yes. Probably a little bit of overstatement because they're probably more informed than the other population, but I think close enough.

CHAIRMAN CANTILENA: Okay. So your answer is, yes, that it would be generalizable.

DR. TINETTI: I say yes.

CHAIRMAN CANTILENA: Okay. Dr. Giudice.

DR. GIUDICE: Yes.

CHAIRMAN CANTILENA: Dr. Trussell.

DR. TRUSSELL: Yes.

CHAIRMAN CANTILENA: Dr. Tulman.

DR. TULMAN: Yes.

CHAIRMAN CANTILENA: Dr. Lockwood.

DR. LOCKWOOD: Yes.

CHAIRMAN CANTILENA: Dr. Benowitz.

DR. BENOWITZ: I would say acceptable, yes. I do share the concerns about a family practice

clinic being a little bit different. The fact that 74 percent of these women had some college education is not the usual user, but there were enough in the subgroups that I think we could extrapolate and say it's acceptably generalizable.

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: Yes,

CHAIRMAN CANTILENA: Any comments?

DR. STANFORD: No.

CHAIRMAN CANTILENA: Okay. Dr. Uden.

DR. UDEN: Yes, with other language provisos.

CHAIRMAN CANTILENA: Dr. Crockett.

DR. CROCKETT: Yes. However, I have some other concerns. One is the illiterate population, that the results may not be generalizable to them.

My second concern is for off-label use potential, which was not addressed in the AUS data at all.

And thirdly, if we're going to generalize the data from the actual use trial, we have to remember that there were a significant number of

patients that did not see this as a secondary form of birth control; that intimated that they may use it as a primary method of birth control. And so if we're going to generalize the good points, we need to generalize that also.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: Yes, with the appropriate training that's coming along with the CARE Program that is described by the sponsor.

CHAIRMAN CANTILENA: Okay. Dr. Patten.

DR. PATTEN: Yes, with the proviso that the overall population of potential users is a very diverse population and --

CHAIRMAN CANTILENA: I'm sorry. Can you speak up?

DR. PATTEN: Yes. With the proviso that the overall population of potential users in the U.S. is very diverse in terms of language, and so consideration needs to be given to that situation.

CHAIRMAN CANTILENA: Okay. Dr. Macones.

DR. MACONES: Yes.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: Yes, to the extent that's I think reasonably possible.

CHAIRMAN CANTILENA: Okay. Dr. Lipshultz.

DR. LIPSHULTZ: Yes.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: Yes, if there's more educational effort directed to other ethnic minority groups.

CHAIRMAN CANTILENA: Dr. Hager.

DR. HAGER: My answer is yes, although I still am concerned about the younger adolescent, the low numbers included in the AUS, and the literacy information. This is a very high risk group of young women who deserve our attention as much as those who would attend family planning clinics and have college degrees.

And so I'm concerned that there is not as much information both as to ability to follow the directions, effectiveness and follow-up among that population. And so my answer is yes, but I think we need more information from that group of patients.

CHAIRMAN CANTILENA: Okay. Thank you, Dr. Hager.

Actually my vote on this will be no for the reasons I think Dr. Hager just stated and Dr. Crockett and Dr. Benowitz. There were enough segments of the population studied which really did not do well, and I think when we generalize this out I have concerns because the study was really done in a somewhat artificial environment, and I understand the limitations on an actual use.

But I think we could have had it more actual and in an actual use. So I'm not convinced that as in terms of information we have on hand, that it would be generalizable to the general population.

So the vote tally for Question No. 2 is 27 yes and one no.

Okay. I think what I'd like to do here to speed things along a little bit is to do Question 3 by a show of hands, and then depending on how the vote comes out, we will have to identify those individuals voting, and of course, after the vote you are free to comment as well.

Number 3, based on the actual use study and literature review, is there evidence that non-Rx

availability of Plan B leads to substitution of emergency contraceptive for the regular use of other methods of contraception.

Let us word this correctly. Okay. We are going to compromise. Dr. Templeton-Somers is very persuasive, and for her ability to record the minutes accurately, we'll just go around the table. I think it will be easier for her.

And, again, it's a yes/no, and then your comments if you feel like you need to comment, and we'll start over on this side. Dr. Hager.

DR. HAGER: No.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: No, based on some of the contraceptive behavior studies presented this morning by the FDA.

CHAIRMAN CANTILENA: Thank you.

Dr. Lipshultz.

DR. LIPSHULTZ: No.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: No.

CHAIRMAN CANTILENA: Dr. Macones.

DR. MACONES: No.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: No.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: One way or another, no.

CHAIRMAN CANTILENA: You don't have to speed. I'm going fast, but please don't feel rushed.

(Laughter.)

CHAIRMAN CANTILENA: We have plenty of time. In fact, we're planning on ordering supper in.

Dr. Crockett.

DR. CROCKETT: I'm going to say no. However, the AUS, the literature review didn't lead us to think that. However, the public testimony did, which I think is very important because those are high literacy people speaking.

And the other point I'd like to make is I don't think that the AUS and the literature review will accurately reflect what the true over-the-counter use would be, and I would suspect that the substitution of EC for regular use of other methods might be higher than we're led to believe in these

studies, which also have, as I said before, an educational and an accountability component built in which change behavior.

CHAIRMAN CANTILENA: Okay. Dr. Uden.

DR. UDEN: No.

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: No, but I also think that post marketing surveillance is warranted because there are enough different variables, and I will say no imbalance because there was one of the studies that showed some possible substitution.

So I think that post marketing surveillance is important.

CHAIRMAN CANTILENA: Dr. Benowitz.

DR. BENOWITZ: No.

CHAIRMAN CANTILENA: Dr. Lockwood.

DR. LOCKWOOD: No, but in view of the UCSF study, I also agree that post marketing analysis would be very important.

CHAIRMAN CANTILENA: Dr. Tulman.

DR. TULMAN: No.

CHAIRMAN CANTILENA: Dr. Trussell.

DR. TRUSSELL: No, and in fact, the evidence would suggest the opposite.

CHAIRMAN CANTILENA: Dr. Giudice.

DR. GIUDICE: No.

CHAIRMAN CANTILENA: Dr. Tinetti.

DR. TINETTI: No, but I agree with Dr. Crockett's extra comments.

CHAIRMAN CANTILENA: Dr. Hewitt.

DR. HEWITT: No.

CHAIRMAN CANTILENA: Dr. Greene.

DR. GREENE: No.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: No.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: No.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: No, but I also think post marketing surveillance is a good idea mostly because you don't want to see people stop using barrier contraception.

CHAIRMAN CANTILENA: Dr. Blaschke.

DR. BLASCHKE: No.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: No.

CHAIRMAN CANTILENA: Dr. Emerson.

DR. EMERSON: No, but I just say that all of this should be done carefully because just having failed contraception, it might not be unusual for people to change their methods.

CHAIRMAN CANTILENA: Dr. Berenson.

DR. BERENSON: No.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: No.

CHAIRMAN CANTILENA: Dr. Montgomery Rice.

DR. MONTGOMERY RICE: No, but I agree partly with Dr. Crockett. I think our speakers definitely gave some indication that there may be some use or substitution, and I think in the labeling in that package insert thing that has all of that information that there should be something that lists all of the appropriate available forms of contraception.

CHAIRMAN CANTILENA: Okay. Thank you.

And I also vote no, and I would second

what was said by Dr. Tulman. There is the possibility for that with the San Francisco study, but only a possibility, and the fact that this is an NDA, Curt, and it's on a switch, then you'll automatically follow with a post marketing surveillance, you know, because it's a switch product.

DR. ROSEBRAUGH: That's something we'll talk over with the sponsor.

CHAIRMAN CANTILENA: Okay. I thought it was automatic if you --

DR. ROSEBRAUGH: Oh, yeah. I'm sorry. With NDA, right, there is post marketing surveillance. Sorry.

CHAIRMAN CANTILENA: Okay. So the vote tally to Question 3 was 28 yes and zero -- excuse me. Sorry. That will be two sodas you owe me, Karen. One because it was unanimous and two because -- okay. So the vote total is zero yes and 28 no.

Okay. Question No. 4, do the data demonstrate that Plan B is safe for use in the nonprescription setting?

And, again, this will be yes or no with

your reasons, and we'll start on this end with Dr. Montgomery Rice.

DR. MONTGOMERY RICE: You know, you could start in the middle sometime, but --

(Laughter.)

CHAIRMAN CANTILENA: If you think I have a hard time keeping track of one end or the other, it would be chaos in the middle. Sorry.

(Laughter.)

DR. MONTGOMERY RICE: I do believe the data does support that Plan B is safe for use in a nonprescription setting.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes to the question, and because of the effect on reducing unwanted pregnancies I would say that it's safer than not using it.

CHAIRMAN CANTILENA: Dr. Berenson.

DR. BERENSON: Yes.

CHAIRMAN CANTILENA: Dr. Emerson.

DR. EMERSON: Yes.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Yes, I would say it's

extraordinarily safe.

CHAIRMAN CANTILENA: Dr. Blaschke.

DR. BLASCHKE: Yes.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: Yes.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: Yes.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: Yes.

CHAIRMAN CANTILENA: Dr. Green.

DR. GREENE: Yes.

CHAIRMAN CANTILENA: Dr. Hewitt.

DR. HEWITT: Yes.

CHAIRMAN CANTILENA: Dr. Tinetti.

DR. TINETTI: Yes.

CHAIRMAN CANTILENA: Dr. Giudice.

DR. GIUDICE: Yes, with a wide safety margin.

CHAIRMAN CANTILENA: Dr. Trussell.

DR. TRUSSELL: Yes.

CHAIRMAN CANTILENA: Dr. Tulman.

MS. TULMAN: Yes, definitely.

CHAIRMAN CANTILENA: Dr. Lockwood.

DR. LOCKWOOD: Yes, with statistical certainty.

(Laughter.)

CHAIRMAN CANTILENA: Well, that's something we haven't had a lot of today.

(Laughter.)

CHAIRMAN CANTILENA: Thank you very much.

Dr. Benowitz.

DR. BENOWITZ: Yes, and I think because no one else has done it, I think it should be on the record in light of some of the comments. I would just say why. It's short-term use only, regular use of this product for contraception in some studies; for planned contraception it has been safe even at much higher doses. There is a long track record of safety of progestin only oral contraceptives, and the post marketing surveillance is totally clean. So I think it's very safe.

CHAIRMAN CANTILENA: Thank you, Dr. Benowitz.

Dr. Stanford.

DR. STANFORD: Yes, safe for the women.

CHAIRMAN CANTILENA: Okay. Dr. Uden.

DR. UDEN: Yes.

CHAIRMAN CANTILENA: Dr. Crockett.

DR. CROCKETT: I would say yes. I'm sure that it's safe for maternal use. I have not seen enough data to determine if it has any long-term effects on fetuses that are conceived as failures of this method of contraception. So I would suggest that as a post marketing strategy that we collect data on the babies that are born.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: Yes.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: Yes.

CHAIRMAN CANTILENA: Dr. Macones.

DR. MACONES: Yes.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: Yes. I've been on this committee, the Nonprescription Committee, for almost four years, and I would task this to be the safest produce that we have seen brought before us.

CHAIRMAN CANTILENA: Dr. Lipshultz.

DR. LIPSHULTZ: Yes.

CHAIRMAN CANTILENA: Dr. Lam.

DR. LAM: Yes.

CHAIRMAN CANTILENA: Dr. Hager.

DR. HAGER: Yes. I would like to see continued post marketing evaluation of the pregnancies, the failures, and also more information on the ectopic pregnancies because I think we can enhance our data bank by having that information.

CHAIRMAN CANTILENA: Okay, and I also vote yes, and I would just second the comments of Dr. Benowitz and also actually Dr. Hager.

The vote on Question 4 was 28 yes and zero no.

Question No. 5: are the plans for introduction of Plan B into the non-Rx setting adequate with respect to consumer access and safe use?

If no, what other options would you recommend?

And here I think what we're getting at is, you know, points of sale, how the drug is sold, and so

those are the kinds of things that you can comment on.

So are the plans adequate with respect to consumer access and safe use? Dr. Hager.

DR. HAGER: Well, I don't want to take a lot of time, but we've talked about this quite a bit today, and my concern, once again, is for adolescents. My concern is the pricing, and I think the sponsor has kind of danced around this issue of we intend to price this drug so that it is not used excessively, and when that is done, in my opinion, there is the risk of pricing out a large group of women of low socioeconomic status who are economically deprived.

And so I have significant concern about that, and that leads me to vote that the plans are not currently adequate.

CHAIRMAN CANTILENA: Okay. I think for a point of clarification, if I'm correct, the FDA does not control the pricing issue, but they can stipulate in terms of the ages required for sale, and it's my -- is that true? I see some people going no.

DR. HAGER: Well, excuse me for interrupting, but I think that the FDA can alter the

problem of pricing affecting access. Is that not true?

DR. KWEDER: No. We are not able to weigh in at all on pricing other than to perhaps make sure that the company is aware of the comments that we've made, but we have absolutely no authority on pricing.

DR. HAGER: Okay. Then my comments are directed to the company, I guess.

CHAIRMAN CANTILENA: Okay. Can you talk about, Sandy, in terms of the age? What are the ages as, you know, proposed here in terms of, you know, legal sale? Are there any restrictions to age as proposed?

DR. KWEDER: For the most part we usually label the drug for use in general as it has been studied. In some conditions, we put an age restriction on it because there has been an age restriction in the trials. In some, that would be typical, for example, in an antihypertensive that was studied in adults. You know, these are prescription products. We would limit the indication to adults partly because the treatment of hypertension in

children is a little bit different.

This is a product that currently does not have an age restriction in the prescription form. So in general, we would not have reason to impose an age restriction for the product unless there were specific reasons to do so.

Historically for all oral contraceptives, we do not have an age restriction because most of the studies are done in a wide range of ages, and we have considered women of reproductive age are capable of reproduction as one group.

CHAIRMAN CANTILENA: So when you say that you've approved drugs according to the study population, in the actual use study here is that what you would then use? Because, you know, I think it was down to age 14; is that correct?

DR. KWEDER: We would probably not put a specific age limit on it, yes.

CHAIRMAN CANTILENA: Okay.

DR. KWEDER: But Steven wants to add.

DR. GALSON: If members of the committee feel that this drug should be restricted according to

age, we'd like to know it, but what Sandy said is valid.

CHAIRMAN CANTILENA: Okay. Well, then, Dr. Hager, you know, you've heard that they have no control or authority in terms of how much the drug will cost. Perhaps you'd like to comment on the ages that it's available for.

DR. KWEDER: Actually, let me also add to that. When you're talking about a product that's over the country, imposing a specific restriction on age is somewhat difficult. There are not very many products of that nature.

It's much easier or it's a little easier for a prescription product because the pharmacist is there. Imposing an age specific restriction really puts the burden on the pharmacist or the store carrying the product to check the age of the purchaser.

CHAIRMAN CANTILENA: Right, but a lot of pharmacies also sell cigarettes.

DR. KWEDER: Exactly, exactly.

CHAIRMAN CANTILENA: So it's not

impossible.

DR. KWEDER: Right. It's not impossible, but you know, in considering that, we would weight the pros and cons of access, but yes, it is not impossible. It's done for Nicorette and nicotine replacement products because it is also in place for tobacco products, but again, that's not something that we enforce. That's something that's voluntary on the part of the pharmacy.

CHAIRMAN CANTILENA: So then you would not have the authority to then require that they check the age of whoever is buying this?

DR. KWEDER: It's something that we would discuss with the company.

CHAIRMAN CANTILENA: Okay, and that is not the same as the process in Canada, you know, behind the counter?

DR. KWEDER: That's not the same.

CHAIRMAN CANTILENA: Okay.

DR. KWEDER: The Canadian system of behind the counter is not a model that we specifically have, but we have many programs where, for example, as the

company is proposing here, something that might achieve some of the same purposes by where the product is placed.

CHAIRMAN CANTILENA: Well, Dr. Hager, now that we've given you a lot more information, would you like to comment on the age issue?

DR. HAGER: I think we are being asked to make a decision about the introduction of the product and age without adequate information. I don't think that the actual use study gives us adequate information for that younger adolescent population, and for me, that is enough of a concern to say that the plans for introduction of Plan B into the nontreatment setting need more evaluation if it is going to be generalizably available to a nine year old regardless, a ten year old regardless of, you know; there's no restriction.

And so that's my opinion.

CHAIRMAN CANTILENA: So then if I can --

DR. WOOD: Just a moment. In the questions that I've got, I don't see anything about age. Where did this come in this question?

CHAIRMAN CANTILENA: It's under access, customer access, consumer access.

DR. WOOD: It doesn't say anything about age though. This question seems to be posed in terms of age. The version I've got doesn't mention age.

CHAIRMAN CANTILENA: The original comment was about the cost and uncertainty with the younger population. So then the question that I asked FDA was are there any mechanisms available for them to control access, you know, based on page, and I'm just asking if you choose to do so, you can comment about how you feel about the age for sale, whether it's an option thing. It's not a yes or no.

You don't have to comment on it. It's just optional because he had to, you know, raise the issue.

Yes, Dr. Berenson.

DR. BERENSON: I would just like to make a point that it is extremely rare that the nine or ten year old has menstrual cycles, and so if we're going to talk about adolescents, let's talk about the mean age of menarche in this country is 12, and I can't

imagine where a nine year old would get $40 to go buy Plan B over the counter and who would buy it for this nine year old.

I just think we need to distinguish between children and adolescents.

DR. HAGER: Well, I'm sorry, but there are young women that age who do start menstrual cycles, and although the numbers aren't large, it is enough of a concern that if there is an 11 year old who is having a menstrual period and becomes sexually active, then she chooses to access this means of emergency contraception, and my only point is not the number. It's that we don't have information available on that younger age population. It just wasn't in the actual use study.

DR. KWEDER: Can I? Lou, let me. Can I just say one of the things that we do, the model that we usually use for over the counter is we would say something like -- on the insert we would say "under age X see a doctor." That would be the most common method that we would use on a product that's generally over the counter.

CHAIRMAN CANTILENA: Okay. Dr. Lam.

DR. LAM: The answer to the question is yes, and I would recommend the sponsor to think about doing long-term study to look at the long-term effect especially after multiple uses, and also would recommend the sponsor to work with pharmacy to make sure that they're not locked up, especially with CVS Pharmacy in the State of New Jersey.

(Laughter.)

CHAIRMAN CANTILENA: We will call the governor of New Jersey right after this meeting.

Dr. Lipshultz.

DR. LIPSHULTZ: I wish I had the luxury of starting over there because I think this is a very difficult question to answer in that there are plans that may be adequate if they work, but they're just plans, and I think some of the words that are used, like "responsible," "reasonable," "easy access by the consumer to a pharmacist," I mean, I'm not sure these can really be done. This is kind of a unique drug.

If we had behind the counter, or whatever they have in Canada, system, I think it would be ideal

to put it there so they were forced to talk to somebody.

So do I think that it's -- are the plans adequate? No, I don't think they're adequate because I don't think they're tested.

CHAIRMAN CANTILENA: Thank you.

Dr. Johnson.

DR. JOHNSON: I think their plans are adequate and reasonable. I think that it should not be pursued as behind the counter. I think there would be less barrier than there is currently, but still substantial barriers in such an access mechanism.

I think that the intention to limit sale to stores that contain a pharmacy is a good one, and I would question -- the only thing that I would have concern or question is as the program is described, the primary educational focus for health care professionals is with OB-GYNs, and I would suggest that your primary focus should be on pharmacists for two reasons.

One is that they're going to be the primary health care professional who will be

interfacing with the consumers who are wishing to purchase this product.

And secondly, as a pharmacist, I can almost guarantee you that their current knowledge of this product is much lower than the current knowledge of the average OB-GYN.

And then finally, in terms of age, I'm not an OB-GYN, but I can't imagine that I would prefer a ten or 11 year old to be pregnant over some hypothetical risk that there might be with a ten or 11 year old taking this product.

So I guess I would feel pretty strongly about not having any age restrictions.

CHAIRMAN CANTILENA: Okay. Dr. Macones.

DR. MACONES: My answer is yes to the question. My only comment would be regarding the hotline that the company is proposing. I think that's going to be a very, very widely used hotline, and I'd really like to see the scripts for the answers to some of the questions that people are going to be calling with commonly be worked out well in advance of this product, you know, potentially going over the counter.

In addition, there was a mention that the hot line could be used for some post marketing surveillance, and I'd also like to see a plan for exactly how that could be accomplished, but I think it is a unique opportunity.

CHAIRMAN CANTILENA: Dr. Patten.

DR. PATTEN: My answer is yes, and I see safe use being linked to changes in the label and the insert that have been suggested around the table, and if those suggestions are responded to, then, yes, safe use.

And I would concur that there should be no age restrictions.

CHAIRMAN CANTILENA: Dr. Williams.

DR. WILLIAMS: My answer is yes. My concerns, of course, the professional and the health care professionals' educational programs that were initiated in the sponsor's presentation, and I'm hoping that that would augment what is given to the media for presentations.

CHAIRMAN CANTILENA: Dr. Crockett.

DR. CROCKETT: I would say no for these

reasons. We heard about other countries that have similar programs and 71 others of the countries have some kind of pharmacist dispensing as a behind-the-counter component, giving education and support to these women. There are only two countries where that's not done and it's truly over the counter, and I saw no data that would duplicate what we could expect to see in the true over-the-counter use here in the United States.

It's my opinion that this class of drug does not belong over the counter.

I have other concerns. We heard some very impassioned testimony this morning about how hard it was for women to obtain this drug because they were afraid to contact people or didn't want to tell what had happened to them. That's one way to look at it, that is, to look at it as a barrier.

But the way I prefer to look at it as a physician and a caring, compassionate physician to my patients is that if you remove the ability or the necessity for that patient to come in and talk to me or just to talk to me, you're removing my ability to

support them, to be an advocate for them, especially in cases of rape or incest; to help them get support and to help them to determine the necessity of the medication that they're taking.

I have concerns that although I believe that this company is well intentioned in decreasing intentional abortion rates, and I wholeheartedly support that, I have a concern that there will be an exploitation of young women's fear of becoming pregnant, and that there will be a tendency for this medication to be used over the counter much more and to sell much more than is really needed, and to consider exposing this large of a population to that kind of open use I think is a bad idea.

And I have a question to end my comments, and that is one of the public speakers mentioned a pediatric act concerning testing of pediatric use, and I would like for somebody from the FDA to explain that a little bit more and to clarify how that would apply to this drug in particular.

DR. KWEDER: This is a pediatric rule for lack of using the longer term, requires that all

products be considered and studied in pediatrics when the population is relevant, when there is a relevant population to be studied.

As I mentioned earlier, historically for oral contraceptives, we have not considered teenagers or adolescents a different population that needs independent study. So we have not previously required specific testing or studies in the adolescent population.

CHAIRMAN CANTILENA: So, Sandy, you would then not apply that rule, you know, for this application?

DR. KWEDER: No, no. We would not be applying the pediatric rule to this application.

That is not to say that we can't ask, that we can't work with the sponsor in any subpopulation of, you know, the general population of users to collect additional data on patterns of use or, you know, whatever may be a topic of interest, but we would probably not apply specifically the pediatric rule to require separate studies in that population.

CHAIRMAN CANTILENA: Thank you.

Dr. Uden.

DR. UDEN: I guess I have to abstain because I can't vote yes or no for this because I don't have enough information. We have an actual use trial which was in clinics and with very literate people. I have no clue what their plan is for people who are not as literate as what has been studied.

We've had come before this committee four sponsors who have said they're going to put together a post marketing support system like the CARE system. I've never seen any data that companies have actually done that and that those have been successful.

I'm sure they're going to do it. They're going to give it a try, but will it be successful? I have no idea.

And then I don't know the impact of having these products sold in grocery stores and gas stations. What's that going to be without them being sold in pharmacies?

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: Based on what I currently know, I think I have to say no. I base that primarily

on the current company Web site, and if some of these changes that we've talked about are made to the package insert and are also reflected in the Web site adequately for informed consent about number one -- my two biggest issues, number one, informed consent for mechanism of action and, number two, the best, accurate effectiveness information.

Then maybe if that all gets filtered out into the hotline and the health care presentations and everything, then I think I could maybe say yes, but at this point I have to say no.

CHAIRMAN CANTILENA: Dr. Benowitz.

DR. BENOWITZ: I think as far as we've heard I would vote yes. I do think that the issue of making counseling available is an important one since we don't have behind-the-counter available and since there are some drawbacks.

What I would like to see is some proactive point of sale signage or something that says "counseling is available, and if you want counseling, see the pharmacist."'

I really think pharmacists need to be more

involved in medications than they are. I think this drug should only be sold in pharmacies or where a pharmacist is available, and I think pharmacists should be educated about this.

I also think that if someone doesn't want to talk to the pharmacist, they should be encouraged to either call the hotline or the Web site rather than just optional because it is an opportunity to educate someone, to make sure they're using the product correctly, to deal with sexual abuse issues and all of the things we've heard about before.

CHAIRMAN CANTILENA: Dr. Lockwood.

DR. LOCKWOOD: Let me just make a couple of points. The first one is that New Haven is the most inaccessible city to air traffic in the United States, and if anybody can do anything about that in the federal government, I'd be very appreciative.

But I --

(Laughter.)

CHAIRMAN CANTILENA: This is the wrong advisory committee for that.

DR. LOCKWOOD: I say that because I'm

going to have to run to the airport to catch the last flight to hartford in about two minutes. So I wanted to sort of make my comments about five and I'll make my comments about six, although I'm not sure my vote will count.

I vote yes, and I think that eh company has done an extraordinarily good job of carefully considering the nuances of this issue, and I support their rationale for locating the product, and I think that their CARE Program is well thought out as well.

I'd also emphasize the need for clear -- no one is going to talk to the pharmacist -- but that there's a clear method for them to access the Web site and/or an anonymous phone number.

And if I could just comment about six, I do recommend a switch in this product to over the counter, absolutely. I think the evidence for efficacy and safety are overwhelming. However, I strongly feel the labeling that I already described ought to be incorporated into it.

Thank you.

CHAIRMAN CANTILENA: Dr. Tulman.

MS. TULMAN: As I'm looking at Question 5, I really see it as two questions, and I would vote yes to both. I think there's the issue of consumer access and the issue of safe use, and I think in safe use, the company, the sponsor has more than adequately demonstrated that the public can use it in the nonprescription setting.

When it comes to consumer access, I would urge it not be a behind-the-counter, but be an on-the-shelf access. I think the notion of having counseling going on in a pharmacy with respect to my colleague sitting next to me, I also live in the State of New Jersey, and in my local pharmacy, there are at any one given moment about 30 people waiting for their prescription, and the least thing I would want is a pharmacist and I to hold a conversation about my sex life in front of my 30 neighbors standing behind me very impatient waiting for their prescriptions.

(Applause.)

MS. TULMAN: So, therefore, I'm not sure that pharmacies are actually the place to do health counseling.

I do applause the company for trying to bring access of this product to the consumer.

CHAIRMAN CANTILENA: Thank you.

Dr. Trussell.

DR. TRUSSELL: Yes.

CHAIRMAN CANTILENA: Dr. Giudice.

DR. GIUDICE: I vote yes, although I have a few comments. One has to do with the age and whether or not we should consider an age restriction. I actually vote not to specify an age restriction.

However, in the CARE Program, in the sponsor briefing document on page 85, the campaign is quoted to appeal to women age 17 to 44, and therefore, I'm just wondering what happens to young women who are less than 17 years old, and I encourage the sponsor to work with the FDA to address that issue.

Secondly, with regard to WEB access here we're making a huge assumption here, and that is primarily for individuals who are more literate and also more affluent, and I would encourage the sponsor again to work with the FDA to enable women who have lower literacy and who are in lower socioeconomic

groups to have more understandable information, and in addition, also to consider translation into other languages.

Thank you.

CHAIRMAN CANTILENA: thank you.

I guess my vote is somewhere between Dr. Lipshultz and Dr. Uden, which would put me formally as a no, but for the following reasons. We're actually going out into uncharted areas. The plan is good, but the effectiveness of the plan is unknown.

With regard to the comment about the age, the application of pediatric rule, it seems to me like the population that we have extremely little information on are the adolescents, and I think this would be an appropriate use of the rule, and a study could be done to assess their behaviors and the information that these individuals will need to use the product correctly.

So I think that that's, I think, a hole in the information that's currently available, and for those reasons I think the plan as currently on the books is not adequate.

Dr. Tinetti.

DR. TINETTI: I would vote that's actually a split vote. It's really two parts. I think it's yes for safe use. I'm concerned that there's not enough work towards getting access off the information for the people who could most benefit from this, and I vote to not have any age restriction.

I guess it's a yes overall, but there was really two parts of the question.

CHAIRMAN CANTILENA: Dr. Hewitt?

DR. HEWITT: I vote yes, and I would like to make some comments about the age restriction. I'm currently a pediatric analyst and gynecologist, and I will try to keep my comments brief, but I do think there are some things in the literature that we can use to help us make a decision about the age.

When we think about teenagers, we need to think about are they different medically, physiologically, and then also are they different behaviorally?

And I do think we have some evidence that we can apply. In terms of the medical physical

difference with teenagers, I think we have lots of information in the medical literature that shows that a progestin would be completely safe for them to use and there's no evidence it would have any impact on their pubital growth or development, and I see no reason that medically a young, adolescent woman would not use Plan B safely.

In terms of behavioral characteristics of adolescent women, we have lots of information about their use of contraception, and most of that information says that they are poor contraceptors, and because of inherent aspects of adolescent development, they are not good at planning ahead. They don't always understand the consequences of their actions, and for these reasons, they become poor contraceptors, and they need access to emergency contraception.

I think it's very important that they do not have to ask a pharmacist to open up a cabinet or to hand them physically the emergency contraception. I think it's important that it's out in the open; it's easy for them to identify.

Oftentimes we have condoms in our clinic,

and we know from use that if we put a condom in a bag and we sit it on the table and say, "Here's condoms if you want to take them," they will take them. They won't ask for them, but we know if it's there, they're much more likely to use them.

I also think that there's also lots of information currently about teenagers using the Internet, and there's been studies that are showing that more and more teenagers are going to the Internet to get information about their health care. So I like the idea of a pharmacist being available, but I don't want that to be a burden or an obstacle to them obtaining emergency contraception, and I think it's important that they have multiple avenues to go to and not to underestimate the power of the Internet for adolescents receiving their health care.

And also I think the 24-hour toll free number staffed by a health care provider is very important.

So I apologize for the length of my comments.

CHAIRMAN CANTILENA: Dr. Greene.

DR. GREENE: I would answer the question ye, and I would suggest with respect to the age requirement that when adolescent women agree to proof of age to a pharmacist before they have intercourse, then that would be the time that they should prove their age before obtaining the product.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: Dr. Hewitt and Dr. Greene have said it all, but I will say yes. The privacy issue, I think is important to consider at the pharmacy, and I think the pharmaceutical company said that they would like this product within the line of sight of the pharmacist, and I think that condoms are no longer in the line of sight of the pharmacist because people are uncomfortable about picking up condoms.

I think for the same reason, these products don't belong in the view of those who are at the pharmacy desk. They should have more privacy for the access of these products.

Secondly, in terms of age certainly, if you are a sexually active ten year old or 11 year old, it's certainly a bad situation, and I've had patients

who are ten and 11 and pregnant, and I think their families and they would have far preferred this option than pregnancy, and it would have been safer. We know that the morbidity and mortality associated with teen pregnancies is quite high.

So there's no question that this is a safer option than the alternative, and that's a term pregnancy.

As a physician, I don't want to have an inflated sense of self-importance, and I don't think that I should act as the gate keeper or barrier to women, teenagers or whatever age accessing medical care for themselves, and this is a circumstance that I think that we need to promote independence of the women and even teenagers accessing something that can prevent or make a determination of their future that they want to determine.

The pricing issue is very interesting, and I think in my experience the government has stepped in for some people who are in certain income brackets and covered over-the-counter pharmaceutical products. If you are a patient who had Medicaid and a pediatric

patient, over-the-counter products are paid for by Medicaid, and I hope that the powers that be can see that this would be one over-the-counter product that could be accessible by federal government supplements.

Thank you.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: Yes, my answer overall is yes. The only caveat is the issue of consumer access, and I think it's crucial for reasons that have already been stated that this not be behind the counter, but needs to be on the shelf or true OTC.

I deal with probably the third or fourth most busy poison center in the United States. Seventy percent are in the pediatric age group. Safety is not an issue here compared to the things I deal with. So it's certainly not an issue about safety.

The only reason for perhaps or at least a major reason for post marketing that I would suggest, post marketing studies in less than 18 years old has to do more with label comprehension and education.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: I also vote yes, and I agree

with the comments of Dr. Giudice. I'd like to see some plans to enhance access and understandability of the product, the use of the product, and so on, for adolescents and for those who don't speak English as their first language.

CHAIRMAN CANTILENA: Dr. Blaschke.

DR. BLASCHKE: My answer is yes. I think the company has a well thought through plan, a care plan and further monitoring plan. It hasn't been tested. It can't be tested, obviously before the product goes over the counter, but I think the plan itself is well thought out.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: I also vote yes, and would advocate strongly against introducing subtle barriers to access, such as raising flags about age and raising issues about behind the counter use. Suggesting that the drug should be only available in the line of sight of the pharmacist seems to me to introduce a privacy concern that I find quite offensive.

I also think that the company should consider advocating its use and patients to have the

drug available at home prior to an emergency contraceptive accident so that they don't have to go out and look for it on a snowy weekend or whatever it is.

I think the issue of behind the counter is false one. The evidence that that has worked in any country is nonexistent, and it has only been suggested, I think, to introduce a barrier to access, which I think would be a disaster.

CHAIRMAN CANTILENA: Dr. Emerson.

DR. EMERSON: My answer would be yes, and I also would be very strongly against the idea that there would be any behind the counter or things. I think that it being readily available on the shelf is very important.

CHAIRMAN CANTILENA: Dr. Berenson.

DR. BERENSON: My answer is yes. I think it is very important that the method if placed over the counter is it's accessible to all women at risk of unintended pregnancy. Any placement of the drug behind the counter or in line of sight of the pharmacist is just creating barriers to its use, and

ultimately it's just going to result in unintended pregnancies.

I also do adolescent gynecology for the last 15 years, and I just had some points I wanted to bring up as a result of this experience. First, I would like to say that the adolescent female is very embarrassed about her sexuality. She's embarrassed to go to the pharmacy and get Tampex. So it would even be helpful if we could make sure that -- this is being said facetiously -- that there is a woman at the checkout counter because it is difficult for he to go by tampons much less emergency contraception and check out from a young male.

The second thing is that although I encourage all of my patients before they are sexually active to actually wait until they meet their Prince Charming or if they decide not to do that, to certainly get on reliable contraception by coming to see me before they start having sex.

It is the are adolescent that ever comes to see me before she has sex the first time. That's because she never planned to have it in the first

place. It just happens, usually on a Saturday night when I'm not available.

The only patients I've had as a rule that come and get contraception from me in advance are the ones that are brought in by their mothers who almost universally have been young teenage mothers themselves, and they feel the experience was so difficult for them that they will place a young 12 or 13 year old that doesn't even have a boyfriend yet on reliable contraception.

So for all of these issues, I feel that we need to decrease barriers.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes on the question. I would, however, mention that all drugs, prescription or over-the-counter, can be and are misused sometimes. I think the issue of the possible potential overuse of the drug like with almost all drugs is a real one, but I would see the tradeoff being that the current under use of the drug is vastly less desirable than potentially some over use.

I do think though that there is a

potential misuse question that hasn't been addressed, and I'd suggest that the company may want to keep an eye out for this because I can see perhaps rarely, but unpleasantly that the drug might be misused by partners as some of the documentation that has been sent to the committee has suggested, and that that's worth keeping a close eye on.

CHAIRMAN CANTILENA: Dr. Montgomery Rice.

DR. MONTGOMERY RICE: I think the plan is adequate, but clearly not as good as it could be. I am disappointed that based on the incidence of unintended pregnancy in the lower socioeconomic age group that the company did not consider that and consider the limitation of access based on socioeconomic status.

I think that making it available at a discount to clinics is not enough because clearly remember what we're trying to do is remove the barrier of the patient having to go to a health care provider or a health care setting to get the prescription, to get the medication.

So I think that the company can do more,

and I fully expect for them to do more if it is approved.

CHAIRMAN CANTILENA: Okay. Thank you.

So in response to Question No. 5 we had 22 yes, five no, and one abstain.

Can I now ask who on the committee has to leave in short order so that we get your votes in before you go? Are you going to leave, Dr. Young. I'm just kidding.

DR. BEITZ: I have a qualifier I would like to ask your help on that would be of help to us in FDA as we move to review the input from the committee and take an action on the application.

We've heard a lot of recommendations addressing labeling change and what we would like your help on is as you address Question 6 to take the way that the "if yes" and "if no" for the things that might be suggested for labeling changes, it would be very helpful from the standpoint of our review if further studies are recommended, say, for example, another labeling comprehension study, if that is needed; if a study is needed, should that be done pre

or post approval? Would that be a condition of approval? Could it be done in Phase 4 or would it need to be done, would the information be critical enough to know prior to approval?

CHAIRMAN CANTILENA: Okay. So if the answer is no, then you want that specified.

DR. BEITZ: Yes.

CHAIRMAN CANTILENA: Okay. Phase 4 or prior to approval.

Okay. Dr. Tinetti, Question No. 6.

DR. TINETTI: Okay. I vote yes to switch from prescription to nonprescription status, and with the caveats of the labeling that we discussed and to eliminate any barriers to access and to encourage as broad access, particularly to vulnerable populations, as possible.

CHAIRMAN CANTILENA: And are there any things that you would specifically want for Phase 4 after approval?

DR. TINETTI: I would like to -- if we could have any effect on -- if there are live births, if there's any long-term evidence for any adverse

effect, but that might be a practical, one thing I'd like to see.

CHAIRMAN CANTILENA: Okay. Anyone else leaving early? Dr. Uden.

DR. UDEN: Do you want to go to Dr. Lam?

CHAIRMAN CANTILENA: Dr. Lam, are you leaving on the same flight?

Use your microphone, please.

DR. LAM: Okay. My answer to Question No. 6 is yes, and I would actually not encourage to include mechanism of action in the label because when a distressed, young woman comes into the pharmacy very apprehensive about the possibility of an unwanted pregnancy, the last thing she wants is to read some scientific jargon on mechanism of action.

CHAIRMAN CANTILENA: Dr. Uden.

DR. UDEN: I vote yes, and we've had a lot of label conversation, and I'm sure you'll find some richness out of that.

CHAIRMAN CANTILENA: How about any specifics for Phase 4 studies post approval?

DR. UDEN: No, I have to think about that

a little more. No specifics.

CHAIRMAN CANTILENA: Okay. Does anyone else have to run to the airport? You could lie to me and leave early, but that's okay.

(Laughter.)

CHAIRMAN CANTILENA: Dr. Montgomery Rice, why don't we start with you for Question No. 6?

DR. MONTGOMERY RICE: Yes, I do believe we should switch. Plan B should be switched from prescription to nonprescription status, and I would recommend additional post marketing studies. So that would be Phase 4 studies after approval, and those would, of course, look at long-term safety issues and actually addressing the question of whether or not people are using it as a primary form of contraception.

CHAIRMAN CANTILENA: Dr. Davidoff.

DR. DAVIDOFF: Yes on the question. Just underscore the importance on the labeling of the timing, the early timing of use .

CHAIRMAN CANTILENA: Dr. Berenson.

DR. BERENSON: Yes, and just with the

labeling issues that we brought up earlier.

CHAIRMAN CANTILENA: Okay. So there's nothing specific for Phase 4 from either Dr. Davidoff or Dr. Berenson, correct?

DR. BERENSON: No.

CHAIRMAN CANTILENA: Dr. Emerson.

DR. EMERSON: Yes, with no specific Phase 4.

CHAIRMAN CANTILENA: Dr. Wood.

DR. WOOD: Yes, and with the maximum access possible. I would suggest if we're going to do any Phase 4 studies that we examine what the residual barriers to use are in order that we can work on removing them.

CHAIRMAN CANTILENA: Dr. Blaschke.

DR. BLASCHKE: Yes on the question, and I think the monitoring plan that has already been proposed is an adequate Phase 4 plan.

CHAIRMAN CANTILENA: Dr. Lewis.

DR. LEWIS: Yes, and on the labeling changes, I think that's already been adequately addressed by our comments with respect to number one.

Post marketing studies, the main thing I would like to see examined is effect on contraceptive practices. I think there were so many long-term studies looking at safety of levonorgestrel that that doesn't need to be emphasized, although, of course, it should never be ignored, but those are my comments.

CHAIRMAN CANTILENA: Dr. Snodgrass.

DR. SNODGRASS: Yes, and no specific long-term Phase 4.

CHAIRMAN CANTILENA: Dr. Clapp.

DR. CLAPP: Yes, and no Phase 4 that I can think of.

CHAIRMAN CANTILENA: Dr. Greene.

DR. GREENE: I would answer yes to the question. I agree that the safety of levonorgestrel including for a fetus exposed is well demonstrated. I'm not concerned about that. I think the agency has received plenty of guidance from the committee to this point about potential changes to the label.

CHAIRMAN CANTILENA: Dr. Hewitt.

DR. HEWITT: Yes, and no other comments on Phase 4.

CHAIRMAN CANTILENA: Dr. Giudice.

DR. GIUDICE: I vote yes, and one comment on labeling, and that is to support mechanism of action at point of service so that women can be informed when they purchase the product, not after they open it and look at the package insert into whether or not they feel comfortable with using this type of medication for the various potential mechanisms of actions that we've described.

And in terms of post marketing, I think that looking at potential changes in contraceptive practices and also continued surveillance on incidence of sexually transmitted infections would be important.

CHAIRMAN CANTILENA: Thank you.

Dr. Trussell.

DR. TRUSSELL: Yes, Plan B should be switched from prescription to over-the-counter status. No recommendations for Phase 4 studies.

CHAIRMAN CANTILENA: Dr. Tulman.

MS. TULMAN: Yes, and no recommendations for Phase 4.

CHAIRMAN CANTILENA: Dr. Benowitz.

DR. BENOWITZ: Yes, and a couple of suggestions. One I agree with or I think someone said this, that there should be some surveillance particularly about adolescent use patterns, adolescent comprehension, safety issues with adolescents. It's something that had been of concern to a number of people, and we may as well get the information to reassure people about it.

I wouldn't hole up approval on any age basis, but I think we should get the information.

And then I still think because we do this for all drugs or most drugs, we should have definitive data on drug interactions, especially if this product is used and may be used as primary contraception by some people, and if it turns out that if they're taking an anticonvulsant or rifampin and it doesn't work, we should know that, and I think that's a study which could also be done Phase 4.

CHAIRMAN CANTILENA: Dr. Stanford.

DR. STANFORD: I still have concerns about the labeling. We've talked about many of them, but I guess because I'm not convinced enough that the

labeling is addressing the actual best effectiveness data and adequately addressing informed consent, I'm going to formally vote no.

I would say if those issues were adequately addressed, then I could vote yes, but I'll record a no.

CHAIRMAN CANTILENA: Dr. Crockett.

DR. CROCKETT: I'm going to say no also, but with some caveats. It's not that I don't support the use of the drug and decreasing the barriers to its use because I do believe it does decrease the intentional abortion rate, and I do believe that it is a health care advancement for women to have access to it.

I disagree that no barrier use is a good thing, and as an OB-GYN I'm going to go down kicking and screaming before I allow somebody to break that relationship between myself and my patients because I value the education component so much in that relationship I have with my patients.

If this is to be marketed as an over-the-counter drug, I do have some suggestions. I would

like to see a better designed actual use trial that more accurately reflects what's going to happen over the counter, i.e., people would be able to get more than one pack at a time, as was restricted in the actual use study without reenrollment.

I would like to see more data on teen use, in particular, and people with low or no literacy levels.

And I would like for some data to be gathered on how many times it's used in a nonindicated manner if that's possible.

Also, if this does go to a pure over-the-counter status, I think we would be doing a disservice to our patients to not include a larger section on education of alternate methods of contraception, including a very strong statement from the company about abstinence and use of condoms to prevent STDs, and this could be a necessary and required portion of the labeling; and that it should be very clear that Plan B is only to be used actually after abstinence and condoms or another primary form of birth control are not used.

And last but not least, I agree with the issues raised about labeling and the truth in labeling mechanism of action. I think as a young woman in this country of childbearing age that truth in labeling is very important, and I think if you don't print on the label that this may affect a fertilized egg in an unfavorable way that you're removing my choice and my ability to make the decision about how I am affecting my body and my pregnancy.

And so I would very strongly agree that that needs to be on the outside of the package.

And thank you.

CHAIRMAN CANTILENA: Thank you.

Dr. Williams.

DR. WILLIAMS: Yes, and ditto.

CHAIRMAN CANTILENA: Ditto with who? Which one? With Dr. Crockett?

DR. WILLIAMS: Yes.

CHAIRMAN CANTILENA: Okay, but she voted no.

DR. WILLIAMS: But yes for --

CHAIRMAN CANTILENA: With the same

concerns.

DR. WILLIAMS: Yes.

CHAIRMAN CANTILENA: The same concerns as Dr. Crockett. But that's a yes vote, correct?

DR. WILLIAMS: That's a yes vote.

CHAIRMAN CANTILENA: Okay. Thank you.

Dr. Patten.

DR. PATTEN: I vote yes, and this is taking into consideration suggestions for modifications to labeling. We've had many discussions about that and also paying attention to the access issues.

CHAIRMAN CANTILENA: Yes, Dr. Macones.

DR. MACONES: I would vote yes, and I would agree with some post marketing studies to look at contraceptive use with this, and I also would agree with Dr. Giudice that including mechanism somewhere in this product label I think would be very important to women.

CHAIRMAN CANTILENA: Dr. Johnson.

DR. JOHNSON: I vote yes for a switch to OTC. I also think that post marketing studies to look

at other contraceptive use would be important so that if they change, then educational strategies can be undertaken.

I think it's important at least that there's a Spanish language available, but that would, I think, then also need to be tested in some form in terms of the comprehension of that label.

CHAIRMAN CANTILENA: Thank you.

Dr. Lipshultz.

DR. LIPSHULTZ: Yeah, I vote yes. In terms of labeling, the only thing is that I would hope that the front would change somewhat so that there was something in addition to emergency contraception because I think that may not be clearly understood.

And I would hope that at some point there is some way to make it less expensive for people who don't have the money to buy it, either with a rebate policy or something like that.

CHAIRMAN CANTILENA: Okay, and are there any specific suggestions for Phase 4?

DR. LIPSHULTZ: No. I think I agree with Phase 4 suggestions.

CHAIRMAN CANTILENA: Okay. Dr. Hager.

DR. HAGER: I am opposed, vote no, and I agree with the, if it is approved, for the post marketing strategies that have already been voiced.

CHAIRMAN CANTILENA: Okay, and the Chair votes actually no on this for the following reasons. The label comprehensive study was, I think, an overall failure. It was approved for the actual use, and there was, I think, an improved track record in the actual use.

However, my concern with the actual use is it doesn't accurately reflect what will likely be the most common setting for this product based on what we've heard. So the actual use was not as close as possible to what we think will actually happen with the drug.

However, I do applaud the sponsor. I do applaud the effort. There is, you know, a need, clearly. I think we can do a lot to improve the communication to the lowering the literacy, which was I think horrible in a word.

And the issues of access, I understand the

FDA has handcuffs on in terms of how much the company charges, but I think that's something that I think you've heard from all of us. We have a concern for that.

So let me read the tally, the final tally. There were 27 votes on Question 6 and 23 yes, four no, zero abstained.

Okay. Are there any other issues that the FDA would like to hear about?

(Applause.)

CHAIRMAN CANTILENA: You're all applauding that you can go now, but until we go, are there any other issues, Curt?

DR. ROSEBRAUGH: I thought they were applauding me. I'm sorry. I didn't know it was because they were going to leave.

CHAIRMAN CANTILENA: I know that usually happens every time you speak in public.

DR. ROSEBRAUGH: It's usually when I'm leaving though.

CHAIRMAN CANTILENA: Not today.

DR. ROSEBRAUGH: I don't think there's any

other issues. I would like to take this opportunity though to thank all of the committee. I know that this was a challenging drug for you all to discuss today. It was a was a very rich conversation, and I think your dialogue will be very helpful with us.

Thank you.

CHAIRMAN CANTILENA: Yes, and I would also like to thank all of the committee members from both committees. You handled this extremely well, very courteous. Extremely helpful, and I would like to thank the sponsor for an outstanding job and being very responsive.

And the meeting is hereby adjourned.

(Whereupon, at 5:17 p.m., the meeting was concluded.)