DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR

REPRODUCTIVE HEALTH DRUGS

Volume II

Wednesday, January 24, 2007

8:30 a.m.

5630 Fishers Lane
Room 1066
Rockville, Maryland

PARTICIPANTS

Charles Lockwood, M.D., Acting Chair
Teresa Watkins, PharmD, Executive Secretary

Committee Members:

Maria Bustillo, M.D.
Ronald Gibbs, M.D.
Daniel Gillen, Ph.D.
Julia V. Johnson, M.D.
James R. Scott, M.D.
Jonathan Tobert, Industry Representative
Lorraine J. Tulman, D.N.Sc., Consumer Representative
O. Lenaine Westney, M.D.

Temporary Voting Members:

Abbey Berenson, M.D.
Paul Blumenthal, M.D.
Eve Espey, M.D., MPH
Melissa Gilliam, M.D.
Paula J. Adams Hillard, M.D.
Johanna Perlmutter, M.D.
Herbert Peterson, M.D.
Diana Petitti, Ph.D.
Bruce Stadel, M.D., MPH
James Trussell, M.D.
Elizabeth Shanklin-Selby, Patient Representative

FDA Staff:

Scott Monroe, M.D.
Lisa Soule, M.D.
Shelley Slaughter, M.D.
Phill Price, M.D.
Gerald Willet, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. LOCKWOOD: I would like to call the meeting to order and just remind everyone that we are going to have a slight change in the agenda in that we need to complete our discussion of cycle control and then, following that, we will move on to extended dosing regimens. But we want to very briefly have the committee re-introduce themselves and then we will have the conflict of interest statement and get going.

DR. WATKINS: Let's start with Dr. Tobert.

DR. TOBERT: I am Jonathan Tobert. I am the industry representative, formerly from Merck and now I have my own consulting firm.

DR. JOHNSON: I am Julia Johnson. I am a member of the advisory committee and I am a Professor at the University of Vermont.

DR. STADEL: Bruce Stadel, retired FDA medical officer, here as a consultant to the FDA.

DR. HILLARD: Paula Hillard, Professor of OB/GYN and Pediatrics at the University of

Cincinnati.

DR. PERLMUTTER: Johanna Perlmutter, obstetrician/gynecologist at Beth Israel Hospital, in Boston, one of the Harvard teaching hospitals, and I am here as a guest.

MS. SHANKLIN-SELBY: My name is Liz Shanklin-Selby and I am a patient rep.

DR. GILLEN: Daniel Gillen, Department of Statistics, University of California.

DR. BLUMENTHAL: Paul Blumenthal, Professor of Obstetrics and Gynecology, Stanford University, consultant to the committee.

DR. TRUSSELL: James Trussell, Professor of Economics and Public Affairs at Princeton University.

DR. WATKINS: Teresa Watkins, the designated federal official for this committee.

DR. LOCKWOOD: Charles Lockwood, chair of the committee and Professor of OB/GYN, Yale University.

DR. WESTNEY: Lenaine Westney, committee member, Associate Professor, University of Texas

Health Science Center, Division of Urology.

DR. ESPEY: Eve Espey, Associate Professor, OB/GYN at the University of New Mexico.

DR. PETERSON: Bert Peterson, Professor of Maternal Child Health and OB/GYN at the University of North Carolina, Chapel Hill, consultant.

DR. BERENSON: Abbey Berenson, Professor of Obstetrics and Gynecology, University of Texas Medical Branch in Galveston.

MS. TULMAN: Lorraine Tulman, University of Pennsylvania School of Nursing, advisory committee member and consumer rep.

DR. SCOTT: Jim Scott, Professor, OB/GYN, University of Utah.

DR. BUSTILLO: Maria Bustillo, member of the committee and reproductive endocrinologist at the South Florida Institute for Reproductive Medicine.

DR. MONROE: I am Scott Monroe, the Acting Director of the Division of Reproductive and Urologic Products.

DR. SOULE: Lisa Soule, Clinical Team

Leader, Division of Reproductive and Urologic Products.

DR. SLAUGHTER: Shelley Slaughter, Medical Officer, Team Leader in the Division of Reproductive and Urologic Products.

DR. WILLET: Gerald Willet, Medical Officer in the Reproductive Division.

DR. WATKINS: We have a few other committee members who have not yet arrived but will be joining us a little bit later on, Dr. Petitti, Dr. Gilliam and Dr. Gibbs. I think that is everyone. I will go ahead and read the conflict of interest statement for those who were not in attendance yesterday.

Conflict of Interest Statement

The Food and Drug Administration is convening today's meeting of the Reproductive Health Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. The committee will discuss current issues that influence the consideration for approval of oral and non-oral; i.e., transdermal and intravaginal

hormonal contraceptive drug products. Issues for discussion will include clinical-trial design, expectation for efficacy and safety outcomes and measures of acceptability of the product to the user, including cycle control. This topic is a particular matter of general applicability.

Unlike issues in which a particular firm's product is discussed, the topic of today's meeting may affect all hormonal contraceptive drug products currently on the market and in development, with the exception of implantable and injectable hormone products and their sponsors.

The participants have been screened for potential financial conflicts of interest with respect to the products and firms that could be affected by today's discussion. In accordance with 18 USC 208(b)(3) full waivers have been granted to the following participants, Dr. Melissa Gilliam, Paula Adams Hillard and Johanna Perlmutter.

Waiver documents are available at the FDA's dockets website. Specific instructions as to how to access the website are available outside

today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussions before the committee, these potential conflicts are mitigated.

Further, with respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Tobert is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Tobert's role on this committee will represent industry's interests in general and not any one particular company. Dr. Tobert owns Tobert Medical Consulting and is a retired employee of Merck.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has 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.

In the interest of fairness, FDA encourages all other participants to advise the committee of the financial relationships that they may have with any firm upon whose product they may wish to comment. Thank you.

Welcome and Comments

DR. SLAUGHTER: Once again, good morning.

[Slide]

I am Dr. Shelley Slaughter. I am one of the medical officer team leaders in the Division of Reproductive and Urologic Drug Products.

As Dr. Monroe did yesterday, I would like to thank you very much for your participation in this meeting. We really will take to heart and have further discussions on all the information that you have provided to us. So, once again, we would like to thank you for your participation.

As you heard in Dr. Monroe's remarks yesterday, this is a general meeting on hormonal contraceptive products, including the oral,

transdermal and intravaginal routes of administration, and we will not discuss other routes of administration such as the injectables.

[Slide]

Our goal in having this meeting is ultimately to seek advice from the advisory committee on issues to be covered in a clinical-trial guidance document for industry that will lead to drug product approval. I would like to say a little bit about a guidance document because we kind of went back and forth between words such as "required" and "recommended." A guidance document is not a regulation. It is not a statute.

To further clarify that, I would like to read a little bit to you from the introduction to these documents that says that the guidance represents the Food and Drug Administration's current thinking on a topic. It does not create or confer any rights for or on any person, and does not operate to bind the FDA or the public. And, an alternative approach may be used if such approach

satisfies the requirements of the applicable statutes and regulations.

In addition to the information included in the clinical-trial guidance for a product seeking approval, we further are asking to hear from you on the types of formal evaluations to be done to assess safety, risk management and effectiveness once a product is approved for marketing.

[Slide]

This slide is going to be modified somewhat. As you heard, we will continue this morning with the discussion on cycle control. Then we will discuss extended dosing regimens, post-approval Phase 4 commitments for further investigation of those serious safety issues, uncommon serious safety issues as well, as I said, the possible role for Phase 4 in investigating effectiveness and risk management. Then we will have discussion of the role and impact of labeling for communications of clinical-trial findings to include product efficacy, risk and other potential benefits. As yesterday, we will lead off with

presentations and then go into discussion by the panel members.

This agenda will probably not be followed exactly as indicated here but by way of introduction I did want to let you know what we will be going over. Following these opening remarks, Dr. Willet, from the Division, will give a presentation on extended dosing regimens. We will then proceed on to the open public hearing where individuals who have previously identified their wishes to speak at this meeting will be recognized.

That will be followed by lunch and then Dr. Petitti's presentation on Phase 4 commitments and the discussion. Then we will have a presentation by Dr. Soule on new physician labeling to introduce the discussion on the role and impact of labeling. We will have a break following that and then we will come back to an overall committee discussion and summary. In that discussion we will probably be asking for some clarifications of some of the issues that were discussed yesterday.

Thank you very much and I will turn the

meeting back over to Dr. Lockwood for the discussion on cycle control.

Topic 4 - Cycle Control Discussion

DR. LOCKWOOD: Thank you. The discussion ended yesterday afternoon with a presentation and then some questions that focused primarily around the issue of creating a standard method of assessing both scheduled and unscheduled bleeding associated with hormone contraception, particularly with the criteria that Dr. Mischell et al. had suggested in their publication and moving away from the WHO Belsey criteria for reasons that were articulated yesterday.

So, the first question to the committee is do the members of the advisory committee agree with recommendations for standardization of data collection and analysis of bleeding in combined hormone contraceptive trials proposed in the article by Mischell et al.

DR. TRUSSELL: Yes.

DR. LOCKWOOD: Dr. Johnson?

DR. JOHNSON: I absolutely support the idea

of having standards for reporting data, and especially analysis of bleeding. I agree that that has definitely been missing and both physicians and patients need to know what we mean when we say bleeding and spotting.

Having said that, is there any other preexisting standard that would conflict with the Mischell recommendations? I know the WHO had put some work into defining menorrhagia, defining abnormal bleeding. I mean, does ACOG have any other standards? I would just hate for there to be more than one standard. If this is the one and only standard for use of contraceptives, then I would say that I would fully support it.

DR. LOCKWOOD: There have been efforts made not only by WHO but actually by other committees and consortia that have attempted to create a better nomenclature for describing abnormal uterine bleeding in general but not necessarily related to contraception.

Actually, I think this is an outstanding set of proposals. I think it moves away from

mixing metaphors with both physiologic and pharmacological processes. And, I like the idea of dividing between scheduled and unscheduled bleeding. The statisticians will correct me, but I think it will lead to more meaningful statistics that actually are more representative of what is actually occurring in the endometrium and the woman experiencing the bleeding.

DR. BUSTILLO: I would just like to put a plea in for getting that information not just for the first cycle but over time perhaps because I think it is a very important clinical piece of information for both the physician and the patient. You know, if 20 percent of the patients bleed on cycle 1, am I still going to bleed on cycle 2 and cycle 3? And, maybe perhaps we should think about some sort of interval at which that should be reported in the clinical trials.

DR. LOCKWOOD: I think that Dr. Trussell talked about the concept of sort of two types of analysis, an analysis of the whole group, which would be important to define sort of the intensity

of unscheduled bleeding that occurs in the initial cycles, but also that a subset of patients need to be followed for at least a year. We talked about the pros and cons of that approach but I think it realistically is the only way to approach it. I think the FDA got that message, hopefully, loud and clear yesterday. Other comments?

[No response]

So, it is clearly the consensus of the group to accept the Mischell et al. criteria.

The second question is how should the Division assess the impact of unscheduled bleeding on product acceptability? That is a little bit harder question.

DR. SOULE: Can you clarify what that question exactly means?

DR. LOCKWOOD: Well, I can give you my assessment but I would defer to the group to come up with their own. I think what we are getting at with this concept is should there be comparability between agents in terms of the degree to which they induce unscheduled bleeding and the degree to which

that affects compliance and, therefore, the ultimate efficacy of the agent? Up till now this has not been-Band correct me if I am wrong, this has not been used in decisions made about approving agents. Correct?

DR. MONROE: It has certainly been a consideration. We consider all the data we get and exactly how it would fit in may vary from circumstance to circumstance. So, I think what we are asking here is are we just going to sort of do it numerically? Like, you could count numbers of days? Are we going to try to associate dropout rates for bleeding reasons as one way of assessing it? Do you folks perhaps advocate trying to address this with a more sophisticated PRO validated instrument because just numbers of days may or may not be a factor in discontinuation? It is those kinds of concepts that we are asking you to perhaps explore and give us your thoughts about.

DR. LOCKWOOD: Dr. Hillard?

DR. HILLARD: I think that standardization is incredibly important and agreeing on the

Mischell et al. guidelines and reporting is a beginning step. I think having better instruments to assess patient satisfaction and such is important, but in many ways I think the decisions are ultimately up to clinicians and to patients so if given appropriate information, a woman would decide is this acceptable or not.

We had many adolescents in my practice who, when given appropriate information about Norplant, for example, when they were told you will have unpredictable and unscheduled bleeding chose to use the product and were very satisfied with it. We had good continuation rates. We had very satisfied patients when they were given that information up front. If they were told, or had they been told that the bleeding might be unpredictable, that is a different statement from the statement that the bleeding will be unpredictable and unscheduled.

So, if patients are given that information I think they will make the decisions. So, my bias would be not to cut off at any given cutoff up

front, but to just present the information in a standardized form and allow clinicians and women to decide.

DR. TRUSSELL: Certainly that was the spirit with which we developed these recommendations. What we thought is that it would be helpful to clinicians in knowing what the truth was so you compare pills and, in counseling women, that is the primary reason for the standardization of the data collection and analysis.

DR. LOCKWOOD: I think one of the things that has become clear in assessing abnormal bleeding associated with Depo Provera and other long-term progestin contraceptives is that in the case of progestin-only contraceptives it is the primary reason for discontinuing contraception. The lower the dose of estrogen in a combined hormonal contraceptive, likely the more dominant the progestational effects on the endometrium and, therefore, the greater the amount of bleeding, and that is roughly borne out by the literature. It is not great literature because this has not been

an area that has been rigorously studied, nor does it lend itself necessarily to that kind of rigor. But it likely will be a bigger problem as lower dose formulations predominate people's usage. Now 18 percent of hormonal oral contraceptives are low dose, very low dose, 20 mcg or lower.

So, it likely will become a bigger issue and I think it ought to become a more important part of the process of evaluating these agents. But it is also vitally important to understand the patient population that you are observing. There are tremendous cultural differences. The acceptability of long-term progestin-only contraceptive varies across the planet literally, and what abnormal bleeding means to one group of women can be entirely different in another group. So, I think that that suggests that it is critical to obtain not only careful empirical-Bif we can say that it can be empirically obtained data about the pattern of bleeding and the amount of unscheduled bleeding. But it is almost more important to assess the patient's response to that abnormal

bleeding.

I think these PRO instruments are the only way to do that and scales are the only way to do that because it will be very important information to know that, although agent A has perhaps a slightly different pattern of unscheduled bleeding, acceptance is much greater. So, I would strongly support the use of these PRO instruments in assessing bleeding.

I think I also agree absolutelyB-being a good libertarian-Bwith Paula about "caveat emptor" and people ought to be made aware of the bleeding patterns, but it ought not to be considered strongly in the approval process. Dr. Blumenthal?

DR. BLUMENTHAL: I think I agree with everything you just said. As Melissa said yesterday, as the approval process of any drug moves forward it is important to get as much information as we can up front and that serves everyone's interests. It serves industry's interests. It serves our interests as providers. And it serves the interests of the patients so when

a product is approved it is a great opportunity to know as much as possible about acceptability and interpretation of numerical and objective findings from the patient's perspective.

I think, again, as we begin to discuss extended cycle regimens, being able to separate, as you said before, the physiologic from pharmacologic issues with respect to bleeding, these much more standardized instruments are going to be very important as we move into extended cycle regimens where there is no real physiologic process.

DR. SCOTT: I was just thinking about what Dr. Johnson said about this classification. I support a standardized classification too. I just wondered did you want this to be standardized definitions for non-contraceptive studies too? Because it has such important implications even for medical student tests, board exams and everything else with the definition of menorrhagia and metrorrhagia, and so on. You could actually apply it to other things, fibroids and everything else.

DR. LOCKWOOD: I think it was not meant for

that purpose. In fact, I think it was very clearly defined around hormonal exposure and non-exposure. But we are working on a new system of classifying abnormal uterine bleeding that is pathophysiologic, unrelated to pharmacological intervention. We are still waiting for that publication of the International Consensus Committee that was formed that is attempting to produce a more logical approach to definitions of abnormal uterine bleeding, and also to unify the world because the United States has one set of criteria, Europe another, Asia yet a third. But this is not meant for that purpose.

DR. TRUSSELL: In fact, these recommendations are limited solely to combined hormonal contraceptive products. They would not apply to progestin-only products because there is no such thing as a cycle. I mean, if you have an 84-day regimen, then that is an 84-day cycle. If you are on Depo Provera there is no such thing, or, if you are on continuous progestin-only pills, there is no notion of a cycle.

DR. LOCKWOOD: There is no hormone-free period with long-term progestin-only contraceptives. Now, the question would come up with continuous use of combined oral contraceptives. Could you apply it in that context, Dr. Trussell?

DR. TRUSSELL: No, not if they are intended to be taken every day forever.

DR. LOCKWOOD: That would mean that if manufacturers are proposing that as the method of use, they would probably have to come up with their own system, which would probably be a very simple system of just quantifying overall amounts of bleeding. Abbey?

DR. BERENSON: I thought the progestin-only birth control pill that we give in lactating women would be considered in these recommendations. Is that not true?

DR. TRUSSELL: No, absolutely not because there is no such notion of scheduled bleeding.

DR. MONROE: Well, the concept of the scales Dr. Trussell can better address than us

because he was a member of the committee that devised them. I would imagine though, taking the concepts and modifying them and adjusting them so that they could be used for various extended dosing regimens could be done to foster some kind of linkage so that an individual using an extended dosing regimen, certainly, would at least be cognizant of what she might expect in terms of bleeding patterns.

So, I think we have heard the message that there should be some standardization. I think what Dr. Trussell and some of his colleagues have proposed seems to be very appropriate certainly for a cyclic pill. I guess the traditional 28 days cyclic pill could probably serve as the foundation to apply it to other types of products, whether it be a progestin only, and I won't mention names, or an extended cyclic pill. I mean, the key isB-and we have a later question on labelingB-how important does the committee feel that information about bleeding, both expected and unexpected is and should that be in labeling? For most of the cyclic

pills it isn't in the labeling for the traditional 21/7s as I recall. We have added such information to the variance of that because there is a lot more consideration.

It is also the committee's feeling that some information about this should presumably be included in labeling where possible for the more traditional 28-day cyclic pill? That isn't our question but it is sort of an offshoot of what you have just--

DR. LOCKWOOD: I am going to take the chairman's prerogative to start this line of inquiry, but I feel very strongly that it should beB-very strongly that it should be --because I think ultimately as doses drop this is going to be a bigger and bigger issue, and it may actually help define which agent providers and patients opt for. Dr. Perlmutter and Dr. Johnson?

DR. PERLMUTTER: I would like to play devil's advocate a little bit. I believe that bleeding should definitely be in the labeling but I am not sure that the FDA should be involved in

whether or not they should approve something according to the bleeding.

DR. TRUSSELL: Everybody agrees.

DR. PERLMUTTER: Oh, okay.

DR. JOHNSON: Yes, I was going to ask Dr. Trussell if he would be willing to now do a new article looking at continuous forms of contraception, be that estrogen and progestin or progestin alone, because I do think that a standard definition of bleeding, leaving out the cyclic part of it, would also be very useful in terms of both information to patients and how they are labeled. So, I would ask your group to get together again.

DR. LOCKWOOD: Traditionally with long-term progestin-only contraceptives it has been a numerical, very simple thing, the total number of days bleeding, spotting and so forth.

DR. JOHNSON: Although the definition of bleeding and spotting probably needs to be standardized, assuming that that can be the same, and that the tracking of bleeding needs to be appropriately done. So, you are right, it would be

simpler than with cyclic medications.

DR. LOCKWOOD: I think that is a pretty clear statement of consensus, labeling, yes; part of the approval process, no; using PRO instruments, yes.

What objective measures beyond hemoglobin and hematocrit, if any and including those, should be employed to assess significant changes in hematological status associated with abnormal or scheduled and unscheduled bleeding? I gave away my bias there. Right?

Is it the consensus of the group that--

DR. PETITTI: There are no symptoms or signs which reliably predict the hemoglobin or hematocrit level and, therefore, I don't think we should try to go there.

DR. LOCKWOOD: Yes. In fact, I think quite the opposite is true. These agents are associated with less bleeding, less anemia. There may be unscheduled bleeding but total volume of blood loss is less than it is with even natural cycles. This is often used as a treatment for abnormal uterine

bleeding. I don't think that this ought to be part of the assessment in any way, shape or form and I think that is the consensus of the group.

We are now going to move to a presentation on extended dosing regimens by Dr. Willet.

Topic 5 - Extended Dosing Regimens

DR. WILLET: Good morning.

[Slide]

My name is Gerry Willet. I am one of the medical officers in the Reproductive Division. In this presentation I will provide a very brief overview of extended dosing regimens for combination oral contraceptives that have been approved by the agency.

[Slide]

The traditional dosing regimen for combination oral contraceptives has been the 21 days on/7 days off regimen. This regimen is shown in the top bar with the 21 days of hormonally active tablets, followed by 7 days of placebo tablets. Within the last 10 years new combination oral contraceptive products have been approved in

which the 7-day placebo period has been partially altered.

One of these products, which is demonstrated in the middle bar, maintains 2 days of placebo but is followed by 5 days of tablets containing 10 mcg of ethinyl estradiol. Two other products have adopted a 24-day on/4 days off approach to dosing, and this is shown in the lower bar where you have 3 days of full combination dose followed by 4 days of placebo tablets.

Two other approved products utilize a dosing regimen where the active combined product is given for 84 days. These products are also called extended-cycle oral combination contraceptives. One of these 84-day active products is followed by 7 days of placebo, and this is illustrated in the middle bar. The other 84-day active product is followed by 7 days of 10 mcg of ethinyl estradiol.

[Slide]

Compared to the traditional 21/7 products, the division has used similar safety and efficacy criteria when evaluating combination oral

contraceptive products that have incorporated additional days of hormone exposure. The daily dosage for these products is usually comparable to or less than existing products. However, because additional days of exposure are added, the monthly exposure for these products may be greater.

[Slide]

This table highlights the benefits and drawbacks in regard to cycle control for the 84-day active regimens. The major proposed benefit for this dosing regimen was that it would result in decreased scheduled bleeding frequency and also decreased overall bleeding. The clinical trials did show a decrease in the scheduled bleeding episodes; however, there was an increase in unscheduled bleeding and spotting episodes, which are demonstrated in the drawbacks column.

Another potential drawback is that the missed period signal of an early pregnancy could be also altered in this regimen, and the product was labeled with this in mind. Of course, we have known for a long period of time that even with the

21/7 products we can get patients who have no period at all and then we have to counsel them in regard to this.

[Slide]

If you peruse the medical literature you may find a number of theoretical benefits that have been proposed in regard to extended dosing regimens. This includes both the products that alter the 7-day placebo window and also the longer extended use products. These theoretical benefits include symptomatic improvement of premenstrual dysphoric disorder or PMDD, premenstrual syndrome or PMS, dysmenorrhea, certain types of menstrual migraines without aura, and epilepsy management, among others.

The only benefit, however, to reach the level of an FDA approval, and that is a secondary indication for women seeking contraception, is through clinical trials for PMDD.

This concludes my brief overview. I will turn it back to Dr. Lockwood and the committee.

DR. LOCKWOOD: Thank you. So, this poses

two sets of questions. The first is if the modified or extended dosing regimen does not expose a woman to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, does a sponsor need to meet any criteria other than the criteria for efficacy and safety required for a traditional 21/7 product? I think pretty clearly the consensus of the group is no.

The second question is if the modified or extended dosing regimen exposes a woman to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, what are the additional criteria that a sponsor needs to meet to support approval for marketing?

So, the presumption here would be that because of the added 7-day period there is, in aggregate, an increase in exposure to pharmacological levels of ovarian steroids.

DR. PETITTI: We are talking about marketing approval and we haven't gotten into

postmarketing requirements or recommendations, or whatever, and I do think that we have been quite unable to predict unanticipated adverse effects of changes which seem minor in hormonal contraception, and the role for finding those sorts of things is postmarketing surveillance.

I think when we get to the postmarketing surveillance section we should keep in mind that any major change in the way in which we administer hormonal contraception has the potential to do things that we do not expect and that there are no tests that can predict the unpredictable.

DR. TRUSSELL: I certainly agree with what Diana said but it is possible that 23a can be true and 24 can be true, in which case the overriding factor ought to be 23a; that is, it gets a total monthly amount greater than one approved product but the same or less than another approved product.

DR. LOCKWOOD: Dr. Tobert?

DR. TOBERT: Well, one way to address this issue would be analogous to the way the FDA has already addressed it with regard to the Evra patch

where plasma levels, as I understand it--I think the estrogen component or maybe both were higher than expected and the FDA put in some warning language. So, that would be another way to do that.

DR. STADEL: If the daily dose is in the same range as the other things, I would just speak in support of what Dr. Petitti said about the impossibility in premarketing to detect a safety difference. I will go further and say that, based on some previous work I have done on safety things, I could argue it either way in theory, that it could actually be safer to have the continuous suppression. I won't go into the details because it is a purely theoretical argument. The main point is that you can't possibly sort out safety issues before marketing.

DR. LOCKWOOD: Dr. Berenson?

DR. BERENSON: I would like to speak against the idea of using a warning label, if it has not been proven to be more dangerous, just because the dose is higher because of these black

box warnings that have been coming out. Many physicians will no longer use a contraceptive that has a black box warning at all more because of the legal climate of our society, and those that do use it feel often that the patient has to sign a separate consent form for it. So, to put a black box warning on things because the dosage is higher over a month, when it is not higher over a day and there is no proven adverse effect, is probably way too cautious.

DR. LOCKWOOD: I don't think you were saying black box, just adding the data.

DR. TOBERT: I have the label here. There is a warning but it is not in a black box. You are right, black boxes are pretty significant. I wouldn't suggest that but plenty of products have warnings.

DR. LOCKWOOD: Right. There are now new labeling requirements and they do have a section on precautions and warnings, and so forth. But that is different than a black box. A black box is reserved for things that have clear health risks.

DR. ESPEY: But the precedent for the black box is the one that is on the Ortho Evra label that I think basically describes this very situation. Where, you know, higher than expected levels of estrogen were found, a black box warning was put on before there was really any proven clinical effect from it. It has had a very chilling effect on clinicians.

DR. TOBERT: I don't know, FDA can say if there is a black box. Maybe I don't have the latest version of the label here but I don't see a black box. I see warning language.

DR. ESPEY: On Evra?

DR. TOBERT: Yes.

DR. BERENSON: I thought Evra has it and there was no controlled study before it went on, and DMPA has it and, again, the data did not prove that the warning would lead to long-term adverse effects. I administer Board examinations to young gynecologists and I can tell you that it stops them cold from prescribing these agents.

DR. LOCKWOOD: I just want to give a little

admonition to everybody to try to avoid using brand names and stay more generic and general.

DR. PETITTI: I would like to speak very strongly in support of what Dr. Berenson said. I believe that we do not know what the mechanism is for the increase in the risk of any of the vascular events; that we are deluding ourselves that we can relate measured hormone levels to an increase, decrease or no change in the risk of venous thromboembolism or any of the other vascular events most prominently, by the way, stroke; and that we should not imply that by putting in a warning about an alleged mechanism that is not established as a mechanism on the label.

If, indeed, we knew that the monthly dose of estrogen was linked with venous thromboembolism, then I think it would justify putting something on the label but we don't know that, and we should take empiric postmarketing endpoint data when we are implying differences in risk of vascular disease.

DR. LOCKWOOD: I think there is consensus

on that by the group, pretty clearly. Dr. Blumenthal?

DR. BLUMENTHAL: I have perhaps one question and one comment. My first question may be to the agency. As part of an application, say, either Phase 1 or Phase 2, we would ordinarily have data on blood levels of a drug under consideration. True?

DR. MONROE: Well, you wouldn't have blood levels if you hadn't done some human studies so, before you would begin your human studies, presumably you would have filed an IND. From some of those very early studies, unless they were done outside the U.S., you would not know what the exposures in people would be because that is the whole purpose of the IND, that you can get it first. Now, during the clinical development program and certainly prior to drug approval the sponsor would submit pharmacokinetic data that would discuss blood levels, and so forth.

DR. BLUMENTHAL: Right. So, as part of that application process then, given pretty

long-term experience now with products with different drug levels resulting in different pharmacokinetics, and so forth, I would think that we would start to be able to see or even start to predict what kinds of studies in the postmarketing phase we would need to do based on some inkling of what the blood levels are going to translate into.

This would also alleviate the need to start thinking about warning labels because of just blood levels as opposed to where you would be able to then say, okay, we have these blood levels and maybe there is a slightly higher dose with a certain product. Those are the products for which we are going to be on guard in terms of thinking in advance of postmarketing studies.

DR. LOCKWOOD: The next question, in reviewing extended regimens how should the division balance a decrease in scheduled bleeding against an increase in unscheduled bleeding?

DR. ESPEY: Well, they don't need to. They just need to give the information.

DR. LOCKWOOD: Exactly. What cycle length

should be used when analyzing cycle control in extended cycle products? In theory there may be no cycle. It is going to be used in continuous fashion. If the sponsor provides you with a specific duration and then requires some hormone-free interval, then that ought to be the interval. Is that the consensus of the group? Great!

DR. BLUMENTHAL: Is there more of an agenda to the question?

DR. MONROE: Yes, a little bit more.

[Laughter]

And, again, it was in an effort to be helpful to the prescriber and the consumer. So, I think, when we think in terms of a traditional monthly cycle, it is fairly easy to conceptualize things, and so forth. But then when you are talking about longer intervals.

And let's say it is an 84/7 or a continuous, to just put those numbers in, then you have to start doing all this mental sort of arithmetic if you are trying to go back and relate

it to a more traditional pill. We wondered if you had any guidance or if everybody can instantly do the mental mathematics and sort of do it.

So, it was put out to try to get your thoughts, again, as the individuals who are talking to your patients because you raised the issue that acceptability is, I thinkB-if I heard you rightB-better if somebody is informed and then they make the decision to go ahead when they understand what is going to happen than when they are surprised.

So, that is really what the agenda of that question was because, again, I don't think your average person thinks in terms of numbers of anticipated bleeding days over a year, the numbers of withdrawals, and so on. So, it was trying to probe from you folks what you think might be helpful. Should one take a yearly product, for instance, and try to go back and normalize it for 28 days or 30, or just put it in, or what? That is really what we are asking of you.

DR. LOCKWOOD: I think I will get things

started by saying that you still have comparability because you can look at unscheduled bleeding with both regimens so you can even compare two different regimens and say that, over the course of a year this particular product, which is a traditional cyclical product, 21/7, produces an average of 12 days of unscheduled bleeding, whereas this extended dose regimen produces 15.

However, and, the labeling can obviously define this, it has no scheduled bleeding or there is only one scheduled bleeding episode, whereas the other product has that.

I think the consensus of this group is that this sort of information is important. It is important for counseling but it ought to be in labeling. Any other comments? Dr. Stadel and then Dr. Johnson?

DR. STADEL: I think I may be restating a little bit what has been said but it seems to me that this is an area where active comparator is great because you get a lot of data on both, and that interpreting the new in relation to the old is

one analysis that would be needed if this is the bleeding cycle with the comparator that is unknown and one has a new product, and then say what is the bleeding experience of people on the new product as compared to the bleeding and cycling with the known product. That, it seems to me, is one analysis that is important.

DR. JOHNSON: I look around the committee and I see some lack of understanding, and I think that is because we are used to using continuous forms of hormonal contraceptives. We are used to progestin-only pills and injectable progestins.

I think when we communicate that to our patients we already do communicate it. Now, having effective labeling and information for patients so they can expect unpredictable bleeding, I think that is very important but I think the cycle length is somewhat of a misnomer. Yes, it is different from what you would expect with 21/7 but, just communicating what is expected of the bleeding. Once we get more information from each of these products and what bleeding is to be expected, then

we can communicate that to our patients.

DR. LOCKWOOD: I think we have covered all this. Any residual questions that you folks might have?

DR. ESPEY: Can I just say that, as a clinician, I think the important thing is I don't usually talk to patients in terms of number of days. It is sort of qualitative. So, the two important things are, you know, qualitatively how much bleeding can they expect and what happens over time. I think those are the two main issues for patient counseling.

DR. BLUMENTHAL: One other quick comment-Bsorry, Mr. Chairman.

DR. LOCKWOOD: Go ahead.

DR. BLUMENTHAL: I am sort of curious about the extent to which, or the detail to which, the agency wants to present this information in a label or in an insert because the print is already small. I don't know if we are talking about contraception for women that are a little older because it gets even smaller.

[Laughter]

But I am wondering. You know, we have talked about presenting information in the label on cycle control. But now we are talking about interpretation in the insert of what these data mean in terms of, say, getting away from the cycle and just talking about how many days you are going to bleed on an average calendar month because extended regimens allow us to just talk about calendar months instead of sort of cycles.

I am just wondering whether that would become overwrought for a label. Then you have all kinds of different ways that people interpret this in terms of qualitative features or quantitative features and I am thinking that it might get a little involved for the FDA to provide these interpretations of the data in the label.

DR. MONROE: Well, I don't think it is our job to interpret in the way I think you are conveying it. I think it is certainly our job to communicate to you. We will obviously have to work on this. When Dr. Soule talks to you, you are

going to see that there is going to be a drastic change in the format of labels. If you are not already familiar, hopefully, you will look upon this as a change for the better so maybe this will answer some of your questions.

DR. LOCKWOOD: I think clearly quantitative data present in the label is interpreted by the physician in a comparative fashion and conveyed to the patient in a qualitative way. I mean, I think that slide that we saw with the arrow and the different things, that is actually how you communicate to patients. They are not interested in--well, you know, this agent has 16.4 unscheduled bleeding days versus the 14.4 there." But I think the information is valid. It is useful particularly as the clinician begins in his or her mind to compare different agents. Paula?

DR. HILLARD: I would just throw out the thought that all of us around the table who are clinicians are very used to playing this role for our patients and helping them to interpret, presenting the information, but also helping them

to interpret and sort out what it means for them. Just throwing out a thought toward the future is that there is a lot of discussion about whether or not combination oral contraceptives should be available over-the-counter, which is another issue for the FDA for the future. Thus, if we are thinking about that as a possibility, perhaps this issue of what is included in labeling, we might view little differently.

DR. LOCKWOOD: Well, we will cross that bridge when we get to it.

DR. WATKINS: At this time we will take an unscheduled 15-minute break, from 9:30 to 9:45. In the meantime, would all of the pre-registered open public hearing speakers please move to the designated open public hearing section so that when we come back we can proceed accordingly? Thanks.

[Brief recess]

Open Public Hearing

DR. LOCKWOOD: If everyone will take their seats, we are going to begin the open public hearing session. Each speaker will have ten

minutes and no more. I believe we do have a method for turning off the microphone at that point. Teresa will call the folks.

DR. WATKINS: The first person is Kirsten Moore.

MS. MOORE: Good morning. We want to thank the scientific staff at the agency for pulling this advisory committee together and having this important discussion.

My name is Kirsten Moore and I am President of the Reproductive Health Technologies Project, a national non-profit advocacy organization. Our mission is to advance the ability of every woman to achieve full reproductive freedom with access to the safest, most effective, appropriate and acceptable technologies for ensuring her health and controlling her fertility. RHTP does not accept any money from pharmaceutical companies or device manufacturers.

We believe each contraceptive method, indeed any reproductive health technology, requires careful analysis of its safety, effectiveness,

acceptability, appropriateness and ethical aspects and that these will vary from person to person and from community to community. To better reflect this variability, we urge the FDA and sponsors to use a more dynamic model in clinical-trial design and labeling.

While we recognize that clinical trials are by nature artificial environments, we are concerned that these environments contribute to poorly informed expectations among women and their healthcare providers about the safety and efficacy in today's world of any particular contraceptive method. When expectations don't match up to reality women are more likely to discontinue their contraceptive use, perhaps exposing themselves to an unintended pregnancy.

The Guttmacher Institute estimates that more than 16 million women are today using some method of hormonal contraception. It defies logic to think this number includes only women who are younger than 35, non-smoking or have a BMI of less than 35. For this reason, we urge entry criteria

to be expanded to reflect the general population. Similarly, we would urge the agency to consider asking for Phase 3 data from a range of service delivery settings, reminiscent of the clinical trials that were run here, in the U.S. for methyl priston medical abortion, to see whether there is anything that could be learned about counseling or follow-up care that might affect efficacy or more timely recognition and treatment of contraindications.

As noted in the briefing document, any woman using contraception weighs a range of factors in finding the best method for her contraceptive needs. A woman may consider a method that is less effective and has an acceptable risk if it causes her fewer side effects or in some other way matches with her lifestyle, for example a method that can be used episodically. For this reason, we urge the FDA not to set a lower limit of efficacy for contraceptive methods.

In short, the more clinical-trial designs can mimic real-world use, the more confidence the

public in general and women in particular can have in their contraceptive method and in the FDA's recommendations. Whether the FDA and sponsors agree to criteria for new trial designs, we strongly urge that the limits of our information be more accurately reflected on current labels.

If women have been excluded from a trial of a particular method, that should be stated explicitly in the product's label. If conclusions about safety or efficacy are drawn from other trials, that should also be stated explicitly.

We would also like to see labeling or FDA-approved patient information better reflect the dynamic nature of contraceptive use and provide women with more and better information about what she might expect from a particular method if she is starting contraceptive use, if she is switching, if she misses a pill or injection, if she has spotting, or when she stops using a particular method. Such information can help contribute to more realistic expectations of hormonal contraception and increase a woman's reproductive

autonomy.

I would just like to say that I know a number of comments were made yesterday about the importance of contraceptive research and that is beyond the scope of the FDA's mission, and that maybe our friends over at NICHD would be able to pick up that slack. I am sure people in this room are aware that the funding at NICHD is going in the wrong direction in order to support that research. So, as an advocate of a national advocacy organization, we would really like to see a greater increase not just of trials of new methods, but really real-world service delivery innovations, patient expectations, education, counseling models so that we can improve women's reproductive autonomy. Thank you very much for your time.

DR. WATKINS: Our next presenter is Amy Allina.

MS. ALLINA: Good morning. I am Amy Allina, from the National Women's Health Network, which is also a national advocacy organization and our mission is to improve the health of all women

by influencing policy and supporting informed consumer decision-making.

The Network was founded more than 30 years ago in the days of the first generation high-dose birth control pills, and we were founded by Alice Wolfson who disrupted congressional hearings to ask why no one was telling women about the risks of these pills, and by Barbara Seamon who wrote the doctor's case against the pill, and by Belita Cowan who worked with both Alice and Barbara to organize a sit-in actually outside the doors of a closed meeting of this committee's predecessor, the Advisory Committee on Fertility Drugs, where risks of pills were being discussed. So, I feel like I need to start by saying I am very glad to be inside the room instead of sitting outside in the hall.

[Laughter]

Also, to say that there have been a lot of improvements since then and, you know, we have lower-dose pills that are substantially safer than the first generation, and we have patient package inserts with the pills which, while they could

certainly stand to be improved in many ways, do give women information that previously was withheld from them.

We also have new ways to use hormones that don't require daily pill taking, and that has been responsive to something that women have asked for and said is important to them and, even more recently, some long-acting methods that are still under women's control, which is another really good innovation that is responsive to what women have been asking for.

As I sort of said humorously to start, the public cannot only hear the FDA discuss these issues the way you all have been doing over the last day or so, but can also give input as we are doing now. So, those are all really important advances I think, and I am going to give you some input on the questions that you have been discussing from the perspective of a consumer advocacy organization.

With respect to clinical-trial design, we do agree with the committee's sort of basic

sentiment that entry criteria for clinical trials need to be more reflective of the real world and, certainly, removing exclusions that aren't exclusions from use makes sense, particularly with respect to BMI. Women 20-29 are almost 3 pounds heavier than we were in 1960; women 40-49 are almost 25 pounds heavier. The mean BMI for adult women is now more than 28.

We have some indications that this has real implications for safety and efficacy of oral contraceptive use by those heavier women. There was a 2005 study of women using OCs that showed risk of pregnancy being 60 percent higher for women with a BMI more than 27.3 and more than 70 percent higher for women with a BMI over 32.2. There are also some safety concerns. Just this month there was a European study released that showed that women with a BMI of more than 30 had 5 times the risk of blood clots. So, this is a pretty critical health concern for women when it comes to OCs.

With respect to study-participant satisfaction, we do support the inclusion of

validated patient-reported outcomes in labeling. We would particularly like to see this address something that I don't think has come up yet in your discussion, which is the effect of OCs on libido. Studies have been back and forth about this and it is a recurring complaint from some women. So, if we could get more information about it, I think that would be very, very helpful.

With respect to the contraceptive efficacy and risk/benefit assessment discussion, like most of you, we are comfortable with seeing the pregnancy rate creep up a little bit if it is a product that offers a proven benefit, either in decreased health risks or some other quality that women value like user control or something else. But we do have to have data so that women can make informed decisions. They need to be able to weigh the relative merits of these products in the context of their lives and that can't be done without data.

On cycle control, I guess all I wanted to say there is that we agree with you on that as well

on the need for standardization. We like very much the suggestions that were made in Dr. Trussell's presentation and the Mischell paper and think, like some of you said, that it is also needed for extended dosing so that we can better understand what role that is playing in women's discontinuation and also just so that women can compare what is known about different methods and have a better understanding of what to expect.

On Phase 4 commitments, and this is the last thing I am going to be commenting on, I wanted to say that we do believe that for new doses, for new chemicals, for new mechanisms of delivery post-approval observational studies should be standard. All these products have some risks for some women and we aren't going to be able to quantify most of those in a Phase 3 trial.

Then we are left with the FDA's AERS system which is passive and incomplete and probably would be generous to call it inadequate. We have seen not just clinician's confidence but women's confidence in products may be shaken by information

that catches us by surprise. We were just talking about what happened with the patch and I think that is unnecessary.

So, when we can't get the information we need in a Phase 3 trial we need to get ahead of the problem and if we can do that we can avoid what Dr. Gilliam was talking about yesterday in terms of some of the some of those boom-and-bust cycles. I think standardizing some Phase 4 studies that will look at the problems so that, if and when problems do arise, we will be in a position to respond with good information. That is going to be to the benefit of both clinicians and women and, I would argue, also to manufacturers. Thank you.

DR. WATKINS: Our next presenter is Susan Wysocki. Has she arrived? No? Then we will go forward with Beth Jordan.

DR. JORDAN: Good morning. My name is Dr. Beth Jordan. I am an internist and medical director of the Association of Reproductive Health Professionals. ARHP was founded in 1963 and is an international professional association whose

members include physicians, advanced practice clinicians, researchers, educators and advocates, all with expertise in reproductive health research or practice.

On behalf ARHP and its 11,000 core members, I am pleased to provide some comments before the Food and Drug Administration's Advisory Committee for Reproductive Health Drugs. For purposes of disclosure, ARHP is a 501(c)(3) non-profit organization and is supported by unrestricted educational grants from many foundations and companies. We also receive individual donations from those interested in supporting evidence-based research and education. Relevant to this committee meeting, ARHP has current unrestricted educational grants from Ortho Women's Health and Urology and Wyeth Pharmaceuticals.

ARHP is a leading source of education and information on reproductive health issues, and is accredited by the Accreditation Council for Continuing Medical Education, ACCME, to provide

continuing medical education and health care providers through a variety of educational programs, meetings, and publications. ARHP advocates for evidence-based research and supports the availability of a wide range of safe, effective and appropriately used contraception for women.

ARHP is pleased that the FDA is reviewing the manner in which hormonal contraceptive efficacy is measured. ARHP's mission is to provide the highest quality evidence-based reproductive health information to healthcare providers and patients.

Choosing when and if to become a parent is one of the most important issues that women face. Patients and healthcare providers alike depend on researchers and regulatory governmental agencies to use the best available science when making determinations of contraceptive effectiveness. For providers to accurately discuss the true risk of pregnancy with their patients who use contraceptive methods, those discussions should be predicated on the highest caliber research.

Given that many respected researchers and

practitioners in the reproductive health field widely criticize the Pearl Index for being a flawed methodological tool, ARHP encourages the FDA to use the life-table methods as a standard for determining pregnancy rates at specific intervals of time. Not only is this method more accurate but, unlike studies using the Pearl Index, one can reliably make useful comparisons of various methods from different studies.

ARHP advocates for the availability of as many safe, effective contraceptive methods as possible to women in the U.S. This includes lower dose options, as well as options for continuous and extended use, which may be beneficial to some women for lifestyle and/or medical reasons.

Many women experience fewer side effects on some of the newer, lower dose pills. While these lower dose pills may be found to be somewhat less effective than higher dose pills, the real-world significance of such a proposed difference is not clear and might well be insignificant in women's lives if these methods

offer them less side effects and, consequently, improved contraceptive adherence.

Every woman is unique and measures of acceptability will vary amongst users. Side effects which are problematic to some women may not be for other women. Culture, history, lifestyle and perception all play a role. For example, unscheduled bleeding while on hormonal contraception may be the number one problem to some women, while others may find mild breakthrough bleeding insignificant compared to other side effects from higher estrogenic compounds.

Information regarding product safety, efficacy and effectiveness needs to be accurately and clearly conveyed to consumers both through product packaging and by the healthcare provider. Risks and benefits associated with different contraceptive products should be discussed between a patient and her healthcare provider, enabling the patient to make informed decisions about her reproductive health care.

ARHP is very concerned about the way in

which providers and package inserts convey risks and side effects to patients and we advocate for clear, simple product packaging. If there are post-approval concerns, ARHP advocates for rigorous follow-up, including postmarket surveillance, in order to gather additional product safety information. Thank you.

DR. WATKINS: Our next speaker is Anita Nelson.

DR. NELSON: Good morning. My name is Anita Nelson. I am a fellow of the American College of Obstetricians and Gynecologists, a national medical organization representing more than 51,000 members who provide healthcare for women. I am appearing here today on behalf of the College to present its concerns and suggestions regarding the approval process for hormonal contraception. In this role, I am an unpaid volunteer.

I will be following my prepared comments, but want to suggest that ACOG looks forward to later commenting on the formal recommendations of

this committee. I am a Professor of Obstetrics and Gynecology at the David Gathon School of Medicine at UCLA, and I am also a member of the speaker's bureau, a consultant, and have done research on just about every major method of birth control that has come out in the last ten years.

The College thanks the FDA for holding this advisory committee meeting and for the opportunity to speak on this issue. The overall message that I wish to deliver to you is that safety and efficacy should be the only basis for product approval. Although product superiority should not be required, the College has concerns about the approval of less effective low-dose combined hormonal contraceptives.

Because of pharmaceutical companies' innovations, today's women have more options than ever for contraception. Finding a contraceptive method that they can use effectively is crucial to women as approximately half of all unintended pregnancies occur among women who are using contraception. The College applauds the

manufacturers for giving American women options and wants to emphasize the need for these methods to be not only safe but also effective in typical use.

Oral contraceptives continue to be the most popular method of reversible contraception in the United States. The women who choose birth control pills do so overwhelmingly for one reasonB-to prevent pregnancy. The other benefits of the pill such as cycle management and reduction of ovarian and endometrial cancer are important but they pale in importance against pregnancy prevention. As physicians, we have counseled our patients that hormonal contraception is a highly effective method of birth control when used correctly and consistently. But in the push for ever lower hormone levels to increase the safety of hormonal contraception are we reaching a point where these contraceptives may be less effective?

This may be the case and could be a reason for concern. Many newer oral contraceptives have higher perfect-use failure rates than the 30-35 mcg pills that have been our gold standard. Will these

higher perfect use failure rates translate into higher pregnancy rates in typical use by the average American woman? The problem may not rest with the dose of hormones in the active pills, but perhaps in the number of inactive pills in each cycle.

Additional studies are vital to answer this question and we eagerly await these data. If these new regimens are less forgiving of the skipped pills that so frequently occur, it is vital that labeling clearly inform physicians and women.

We know that lower-dose extended cycles are growing in popularity among American women and we need to know more about the risk of unscheduled bleeding and spotting with these regimens. In the traditional 21/7 packages unscheduled bleeding and spotting is the leading cause of discontinuation.

So, it is important for us to understand this phenomenon well so we can counsel our patients appropriately. Clinical trials should be required to use standard definitions of spotting and bleeding that reflect the days in an appropriate

length cycle. Labeling should also identify the mean, median and range of days of both scheduled and unscheduled bleeding and spotting.

Now, I have mentioned several points that should be added to the labeling of hormonal contraceptives. Labeling, however, should not be the sole way that clinicians and patients receive important information about these new regimens. The full labeling now is more than 40 pages long and busy clinicians may simply fail to read all of it. Other methods, perhaps including "dear doctor" letters, should be explored by the FDA and by industry.

Finally, the College urges that clinical trials be designed to study the efficacy and the safety of hormonal contraception for all women who use them. Not all women who rely on these contraceptives are 20 years old and weigh 110 pounds. We need data on all women who use contraceptives, the 16-year olds and the 45-year olds. Importantly, we need to know about the safety and the efficacy of use in women who are

overweight or obese, a considerable portion of American women. Clinical trials should include a spectrum of women representative of U.S. women using contraception, with power sufficient to determine efficacy, safety and side effect profiles in these different subgroups.

In conclusion, real-world efficacy and safety are vital. The information American women and their physicians are provided about the safety and efficacy of each formulation must be applicable to all potential users and must accurately reflect in a standardized fashion the more common side effects, especially bleeding episodes. The College's 51,000 members stand ready to help our patients make these important decisions, and both physicians and patients need accurate data on safety and effectiveness to do so. Thank you very much.

DR. WATKINS: Our next speaker is Kelly Blanchard.

DR. BLANCHARD: Good morning. I have the pleasure to be here with the committee. Thanks to

everyone who worked to organize it.

My name is Kelly Blanchard. I am the President of Ibis Reproductive Health. Ibis' mission is to improve women's reproductive health choices and autonomy worldwide. At Ibis we conduct clinical and social science research, as well as policy research, and our aim is to help support reproductive healthcare and policies that are informed by the best evidence.

What I would like to do today is to very quickly share the results of some work that my colleagues and I at Ibis have done which compares the labeling of current contraceptive methods to the best current evidence. I think you have in front of you the longer paper that this is based on but I would like to just give a few highlights and then talk about what we might recommend based on what we found.

The paper itself does address a number of contraceptive methods. I am just going to speak to the parts about oral contraceptives here. Here are three of the major differences we found when you

look at the evidence and look at the label.

Labels recommend a physical examination prior to provision of oral contraceptives. We know from evidence that women themselves may be able to self-screen for contraindications and that exams may be a significant barrier to use for some women, particularly specific subpopulations of women. Of course, we know that many providers have looked at this evidence and now don't require a physical examination. But I think the question here is what is reflected in the label and what that might do to physicians who may not be currently aware of or keeping track of the best, most recent evidence.

The second point here is about breast-feeding women. The label says that breast-feeding women should not use COCs, but the data on COCs and lactation are conflicting. They are not well done. Many guidelines that exist state that if a woman has established milk flow and is otherwise healthy that COC use is fine. Again, that is not reflected in the labeling and may be a significant barrier for women who are postpartum

and are looking for a method, and they are limited from using COCs because of what is inaccurate information in the labeling.

Finally guidelines about when to start your COCs, most labels say the first Sunday or day one of your menstrual cycle. This is somewhat complicated and confusing, and a growing body of data shows that you can probably successfully start your method on almost any day, the quick-start method, but more and more data is coming out about this. Again, it probably limits a number of women from actually using this method. They may not come back at this point. It may be confusing, etc.

Just by way of background, I think a number of speakers have referred to the data the Guttmacher Institute has found. The way this data shows is that after a decrease over time in the number of women not using contraception, in 2002 we have seen an increase in the number of women not using contraception. So, we, at Ibis, are particularly concerned about what might be behind this increase in women not using contraception.

Again, we think part of this, and of course not all, is related to what is potentially in the label and the barriers that that puts in women's way and in physicians' way as well.

We know a lot of data from all over the world has shown that women overestimate the danger of using hormonal methods. There are a lot of myths about hormonal methods, the need to take breaks and things like that. Although the labeling of oral contraceptives might not be the main way that people get that information, it certainly is a way that a lot of people get information and ideally should reflect, again, the best evidence so that we can provide people with the correct data and they can sort of make informed decisions about whether or not to use these methods.

The other thing shown on this slide that is striking is the difference between poor women and women who are not poor, which is an important consideration. Minority women are also not well represented in trials and have higher rates of non-use of contraception. In terms of looking

forward about whom to include in clinical trials, these may be key groups to really try and make sure they are joining the trials and we have more information on particular issues around acceptability, or other things that may change their opinion of different methods and why they would or would not use them.

Just one final point, here are some recommendations related to trials and labeling, again, as I just said, including a more diverse population in clinical trials; including racial and ethnic makeup, as well as women of lower socioeconomic status; and also potentially including-Bgetting back to the question which I think was discussed here about exclusions and what that reflects about exclusions in the label--potentially including moderate risk women, obese women, smokers age 30-34, women with a family history of thrombosis and breast-feeding women because, based on the current data, these women may be completely appropriate candidates for COCs, particularly if they are not interested in using

other types of methods.

The data we have, really, on risks for these women, as we discussed yesterday, it is very hard to have large enough trials to really look at these rare events, but we may be excluding a number of women who could successfully use these methods.

We also need to take into account what is on this slide, the question of what we are comparing to because many of these women in these moderate-risk groups would be at even higher risk of an adverse event if they were to become pregnant. So, again, in terms of labeling, I think this is an important thing that is not in the public consciousness around choosing contraceptives or hormonal methods, which is what are these same risks during a state of pregnancy and I think we could do better about sharing that information.

Also in terms of comparisons, it would also be useful I think, and I am not sure how this would ever be done in a label, but to compare hormonal contraceptive methods to other drugs that women are likely to use regularly. Again, I think

this idea that hormonal methods are so dangerousB-many might agree that they are safer than many drugs that people access over-the-counter on a daily basis and, yet, it is almost impossible to easily find information that compares those types of risks.

I think this is the final slide. In summary, hormonal contraceptive labeling should incorporate recent evidence as well as the recent studies have shown that graphical representation of some of the facets of the label might really help with comprehension. It should incorporate up-to-date and evidence-based information. And, the process for amending labeling should be changed to allow for rapid inclusion of new compelling data.

I think it is interesting, based on a review of FDA procedures, that it is very easy to make a label more restrictive and much more difficult to make a label more permissive. I think that speaks to sort of the general tenor of labeling and what labeling does, which is often to

scare people about things that are very unlikely to happen to them.

Obviously, there are a lot of reasons for that and the label fulfills a number of different functions for a number of different people. I think our interest in thinking about public health and access to contraception would be to try and figure out ways to make that less the purpose and focus more on people getting accurate up-to-date information.

In my last minute, I just wanted to echo a comment made earlier about the evidence for over-the-counter use. I realize that this may not exactly be the right forum for this, but I just wanted to say that it does seem that oral contraceptives fulfill all of the criteria for over-the-counter access, particularly in comparison to other over-the-counter drugs. They are much safer in many instances. Women can self-screen for contraindications. And, we would look forward to either this committee's recommendation or another forum to discuss what the next steps might be, or

what process would need to happen to make that a reality.

Thank you.

DR. WATKINS: I will make one last call for Susan Wysocki. Has she arrived? No? Then, we will go ahead and have Dr. Petitti present.

Topic 6 - Phase 4 Commitments

DR. PETITTI: Well, I actually greatly appreciate the opportunity to speak at this meeting, and think that this is a meeting which has the opportunity to make major changes going forward. Perhaps the meeting is 20 years or so overdue.

[Slide]

I am going to talk a little bit about our potential for improving the way that we gather information on safety and effectiveness after marketing approval.

[Slide]

I put this slide on here to remind me that I have a new position as the Adjunct Professor in the Keck School of Medicine. We don't have to say

the first initials as they do at UCLA, which is also in Southern California.

[Slide]

Right now, as we all know, hormonal contraceptives are approved based on information from a very small number of women. The populations are not, in fact, currently designed to be representative of the women who will use contraceptives in real life. In fact, little is known about the effectiveness of use of hormonal contraception outside the realm of the women who participate in clinical trials.

Since the overwhelmingly most common reason for women to use oral contraceptives is to prevent pregnancy, there really is an opportunity to improve our information about the effectiveness of hormonal contraceptives in the postmarketing arena.

I am going to divide my talk into--talk about the safety and about the effectiveness and what the potential might be for gathering better information in the postmarketing arena.

[Slide]

We actually know a lot about what we can expect about the safety of hormonal contraceptives in the postmarketing arena, much more than for other drugs which are new entities. We know what to look for. We know pretty much what not to look for.

Indeed, vascular events are the most important major adverse event caused by combined estrogen/progestin contraceptives. I mention specifically so that we don't forget that there is ischemic stroke in addition to venous thromboembolism and myocardial infarction. Venous thromboembolism is the event with the highest relative risk in most oral contraceptive users but ischemic stroke is the one that has the most devastating consequences.

[Slide]

There are some very specific issues in the study of the safety of hormonal contraceptives which make it impossible to study them premarketing and difficult even to study postmarketing. The

main thing is that they are rare. They are rare but not uncommon. In other words, they are the kind of event which simply is not ignored within the context of this risk/benefit ratio but is not so common that it would mean that you wouldn't want to use them in healthy women.

The other very important factor about the safety of oral contraceptives in terms of vascular events is that there are proven interactions or, I prefer to say, effect modifiers. These include hypertension predominantly for stroke; obesity predominantly for venous thromboembolism; and cigarette smoking predominantly for myocardial infarction.

[Slide]

I want to make sure that everyone understands this slide and, hopefully, believes this slide, which is that we do not understand the pathophysiology of vascular events caused by combined estrogen/progestin hormonal contraceptives. We, thus, cannot predict ahead of time whether or in what direction a change will

affect these events.

The inability to predict extends to changes in estrogen dose, estrogen type, progestin dose, progestin type, route of administration, cumulative dose, maximum dose, etc., etc., etc. There are no hematologic parameters. There are no intermediate endpoints that can be used to predict whether a change in a given contraceptive will or will not, and in what direction it will, affect these vascular events.

[Slide]

Now I am going to talk about Phase 4, which currently I think should be described as surveillance where surveillance consists of a collection of unsystematic activities. First of all, there is formal surveillance assessing spontaneous reports of adverse events to the FDA.

There is surveillance which consists of the astute clinician who might report an adverse event, either anecdotally to his colleagues or her colleagues, to the FDA or in the form of a case report. Then, there is surveillance which consists

of an interested researcher deciding to conduct a study in response to a report of an adverse event or based on their own observations.

[Slide]

In my opinion, the continuation of this unsystematic approach really invites trouble related to false alarms based on faulty data. Waiting for alarms also invites panic in response, and alarms, whether ultimately false or true, undermine the public's confidence in the regulatory system and in the industry. I think that the pattern has been, in introducing new hormonal contraceptives, to not plan for formal postmarketing studies in hopes that nothing will happen and, in fact, something will happen and what will happen will be something that may or may not be a true alarm, may be a false alarm but causes panic.

If, indeed, we know ahead of time that most of these preparations and formulations will continue to be associated with some vascular events, those vascular events, if the astute

clinician decides, will result in a flurry of reports of, let's say, every stroke that they saw in the first ten patients, or all the first ten strokes in the patients on a new contraceptive are reported to the FDA, giving the appearance that there is a problem greater than in other preparations or formulations that are being newly initiated by women in the same risk category.

[Slide]

So, I believe that we really need to move on. I want to make a point that in the study of effectiveness the old products are as poorly studied as the new products in terms of postmarketing surveillance, and we already know that there are population trends that probably are affective use-effectiveness both in old and in new products that we know very little about.

[Slide]

Now, my recommendation here is that we begin to plan for more Phase 4 studies. Notice that I said Phase 4 studies, not Phase 4 trials, because I think there are a variety of studies that

can be useful in the postmarketing arena that are not currently conducted and that actually do a disservice to the amount of time and energy that goes into premarketing development and approval both for the public and ultimately, I think, for the industry.

[Slide]

Now, I am going to talk about the design of Phase 4 studies of safety first and I am going to put up the classical designs that people mention when talking about Phase 4 studies of drug safety. We talk about experimental studies, case-control studies and cohort studies. And, I am going to spend a fair amount of time talking about designs which use the case-control methodology nested within a cohort.

[Slide]

Phase 4 RCTs are actually--you know, I am having a hard time recalling where anyone would require a large-scale Phase 4 randomized trial in order to study safety whether against a placebo or an active comparison group.

It would be extremely costly if it were large enough to address the issue of vascular event differences, and it would be difficult to choose a single appropriate comparator. The likelihood would be that you would have to look at the new product compared with some range of products, which doesn't make sense in our RCT setting. And, I really actually think that there is no such thing as a simple randomized trial.

[Slide]

So, I am going to limit myself in talking about recommended designs to consideration of case-control, cohort and case-control nested within a cohort studies.

[Slide]

In reality, the typical case-control study design as a stand-alone design is used most often to study exposures that occurred in the distant past for which exposure information is not available, or cannot be reliably retrieved from records or computer-stored data. So, there really is not much of a role of a case-control study in

surveillance outside of being nested within a cohort defined by exposure based on computer.

[Slide]

Now, the main disadvantage of--I'm not going to say this--of the classical case-control study is recall bias. Increasingly, case-control studies which involve direct interview of patients are subject to very low response rates. It is actually quite depressing in the epidemiology field to see response rates in typical case-control studies fall from 90 percent 20 years ago to the 60s today, and this problem is particularly acute among women of reproductive age who tend to have a lot of things going on in their lives. You are better off doing a study in the elderly now than in anyone of reproductive age.

[Slide]

I believe that we have an enormous ability, which was not present 10 years ago and certainly not 20 or 30 years ago, in the United States, to use computer-stored information on drug exposure to combine the best features of cohort and

case-control designs.

A number of HMOs, a number of pharmaceutical clearing houses have assembled databases and have managed to overcome some of the concerns that were present about the quality of that data and ability to actually access patients and women to do direct interviews compared with the past. There has been truly, over the last 10 years, a major change in the quality of this data, in the quantity of this data, and in the ability to utilize this data for studies of drug safety.

[Slide]

When I talk about cohort studies I am going to briefly consider the possibility that one might want to go out and mount some giant safety study with all these products coming on the market. There is the possibility, maybe we ought to go out and do another Royal College of General Practitioners study or another Martin Vessey study, or maybe another Walnut Creek study where you go out and you enroll 50,000 women who are users of hormonal contraception and you follow them forever

to find out what these new products are really about in terms of safety and effectiveness. But I am going to actually reject that design and go right on to computer-stored studies that use computer-stored data.

[Slide]

The problem with the sort of Vessey-like study is that the advantages are that you get comprehensive information about both the things you anticipate and things you don't anticipate. By enrolling women, by interviewing them at the start of your follow-up, you get excellent information on confounders.

You have the ability to include diverse populations because you can specifically organize the study in certain communities. However, it is costly. The time to results is long and the power for rare events remains quite low. You still have ability to recruit numbers on the order of 50,000 or 40,000 or 30,000 or 20,000 and probably not the hundreds of thousands of women that you need in order to address the safety issues that are of

concern for oral contraceptives.

[Slide]

So, I am going to go on to talk about various designs that use computer-stored data and talk about using computer-stored data only, computers supplemented by medical records, and then computers supplemented by medical records with some amount of direct interview of women who have events compared with women who don't have events, chosen in a random fashion. That is the nested case-control design.

[Slide]

There is a tendency of drug-surveillance studies to want to rely only on computer-stored data, and we see a lot of studies now of drug safety which are computer-stored data only. The advantages, of course, are that it is relatively inexpensive. You can get information fairly quickly.

However, for a study of vascular disease it is actually not possible to confirm that the events that are listed as events in some diagnostic

registry are true events. This is a big concern in studies of vascular disease where you really need to make sure, first of all, that the event is a first event. That is very, very important. And, you have to confirm that it is a first event and, second of all, you have to be able to determine that what you called a venous thromboembolism is truly a venous thromboembolism.

This is a big problem with oral contraceptives because there is a tendency to perhaps over-diagnose vascular events in women using oral contraceptives. In computer-stored data the patients are generally very poorly characterized. No matter what someone tells you, they are not going to have reliable information on body mass index and on race/ethnicity in a computer-stored database. And, I say that no matter what they tell you, they really don't have it because it is so hard to collect.

Information on other kinds of confounders is really not presentB-family history, personal history, past history, again the BMI, cigarette

smoking. And it is actually difficult to study effectiveness with the computer-stored data because abortions, even among insured populations, are often not covered events. Even when they are covered events, women have a tendency to want to go outside the system in order to get their abortion and, therefore, they are not reliably recorded in the system. We have had a number of people, when I worked at Kaiser, come to us, wanting to study effectiveness using our computer-stored data and the answer was we can't do it because it is not reliably recorded.

[Slide]

Supplementing computer-stored data with physician records has a number of advantages and the thing that it does. It allows you to determine whether or not the events are confirmed events; whether they are new events. You can obtain some information about confounders from medical records, not necessarily complete. In fact, that is the major disadvantage. When you are looking at effect modification and you need information on effect

modifiers or confounders, you have the lack or inconsistent availability of information on these.

There is actually uncertain accuracy of information recorded in medical records about confounders and, in fact, modifiers. And, paper medical records and talking to the physician are no better than the computer data in terms of studying effectiveness because many women, again, who have a failure on a contraceptive go outside that physician in order to, for example, have a termination.

[Slide]

So, I am going to say that I think the best design for postmarketing studies of the safety of hormonal contraceptives is a combination of computer-stored data with physician records, with direct patient contact where the direct patient contact occurs on a sampling basis, where all the confirmed cases are interviewed directly to ascertain information about confounders, and that a random sample of controls, which would be women also using some form of hormonal contraception who

did not have an event in the same interval, because I think the issue is comparative safety and not whether or not this particular contraceptive has an increased risk of some venous event.

So, I would argue for a computer study where you take all of the women who have a prescription for the new contraceptive and everyone else who is given hormonal contraception during the same interval, where you use sampling techniques to characterize the starting patterns of the controls and the cases.

You probably have a ratio--I haven't done the design parameters, but you probably have a ratio of ten controls to one case given the rarity of these events. This has the potential to characterize patients well, including patients who did and didn't have an event.

You get excellent information on both confounders and effect modifiers. You get accurate and complete information, or at least comparable information between the group that you are interested in, which is the new contraceptive

group, and the old contraceptive, hormonal contraceptive group.

It is relatively expensive but not, in my opinion, prohibitively expensive compared with having your drug go down the tubes because people believe that it is worse than the alternative. The time to information is long, mainly because the time to sufficient numbers of events may be long. And, it is subject to response bias. Again, I mention that getting women of reproductive age to participate in research is an increasingly difficult task.

[Slide]

I am going to talk a little bit about specifics of sources. I think that many studies have been done based on the GCRP database. I think that in that database they have limited ability to do direct contact. There are a number of I think privacy issues with regard to the use of the data that actually make it not as good a source of data for this kind of study in the United States as some of the large databases that are being assembled by

some of the large health plans.

You could have one health plan or you could use a variety. a consortium, of health plans, perhaps a group of health plans or sources of computer-stored data including Medicaid data that organize themselves to be responsive to carry out a variety of safety studies going forward, not just safety studies of hormonal contraception, and I think these are being organized as we speak.

[Slide]

I am just going to say that when you do use a single source of data, if you have a single source of data, it is often much more efficient. You don't have to go through 15 IRBs. You have great ability to trust the study planners assertions. I have been involved in a number of collaborative studies where one or more of the entities participating in the study did not actually have in their computer the data that they said they had in their computer, or were not able to access in the ways that they described the records needed to conduct a study. So, I mention

that based on my own personal experience over the three decades that I have been working in this field.

Another disadvantage of using a single source or using a limited source of data for computer data is that there often can be a very restricted set of contraceptives, hormonal contraceptives, in the comparison group because of limitations on the formulary.

If you go across a variety of sources, then it is likely that you have a greater mix of comparison hormonal contraceptives and I think we can't simply say, I have a group of patients who have been exposed to the new hormonal contraception and my rate of venous thromboembolism is 22/100,000, and the literature says that the rate of venous thromboembolism in hormonal contraceptive users is 44/100,000, therefore, my product is equally safe or even safer. I think that that kind of data is not useful at all. It is highly misleading. You have to have a comparison group of hormonal contraceptive users who are

contemporaneous.

[Slide]

So, again, I would recommend that the ideal postmarketing study of safety, designed to look at the vascular events that have been found in users of hormonal contraceptives, would be a computer-based prospective cohort study where the new product would be combined with all old products. I put in newly initiated but I want to take that out. I thought about it on the airplane. I think you should just take all-comers and then post-stratify after doing informative sampling.

The data should come, in my opinion, from multiple sources in order to increase diversity of the population of users and to assure a representative mix of hormonal contraceptives. And, I believe we need to have confirmation of the cases using records and experts, working with specified criteria, who have been blinded to the use.

[Slide]

I think we need to collect information on

confounders and potential effect modifiers by direct patient contactB-and I got into the real nitty-gritty here--using a nested or probably a case-cohort design with unmatched controls so you don't end up with a lot of restrictions in the analysis phase with substantial over-sampling of the controls. And, the nesting or the cohort design decreases cost and the lack of matching and the over-sampling make it possible to post-stratify.

[Slide]

Then, I think that there are a number of advantages. You can't use this design to study effectiveness. I don't think you can because you have restricted the cases in the controls to people who are either failures or non-failures on the method.

[Slide]

I think that it is going to be difficult to mount a study that will definitivelyB-when I say definitively, meaning that you have a really narrow confidence interval on some relative risk of

1.0--of a new product compared to another because the rarity of the events and the power of any feasible study design is low. But I think you can prespecify a certain range for which you are willing to accept equivalence, much like what we have in the clinical-trial design.

I think that if it is hard to study whether or outcome there are differences overall, the ability to determine whether or not there are differences in the interactions is even more limited, or even to study whether there are interactions. If you look at the papers that show interactions of hormonal contraception with these various factors, they are based on very small numbers, extremely small numbers with high relative risks but very wide confidence intervals.

I would say that the main reason for using hormonal contraception is pregnancy information. I believe that as we conduct studies of safety we should use this method of computer-stored data to gather more information about the comparative effects on effectiveness.

[Slide]

I think you can design a study of safety that would use the same population to look at effectiveness and use-effectiveness because you need much smaller numbers. The events of pregnancy are measured on a scale of 100 not a scale of 100,000 and you can imagine some kinds of sampling in order to accomplish this.

You need a cohort design with regular patient contact because, again, of the limitations of computer records to ascertain pregnancies reliably. You also I think have to think about response rates. People who fail or have a problem on a product are actually not as willing to talk to you as people who perhaps have had a wonderful outcome with that product. So, I think response rates have to be kept. The same, if you have a comparative trial that might not be a big issue. And, that is all I had to say.

DR. LOCKWOOD: Thank you. Questions about the presentation? Yes, Dr. Scott?

DR. SCOTT: Great talk, Diana, particularly

in pointing out the pitfalls of database studies. There certainly are and they can be biased, and I think they have to be validated, like you said, with physician records or with patient interviews because it depends on who puts in the data and a lot of things that go to the accuracy.

What I wondered about is that follow-up studies for safety have been very haphazard with everything, every drug. I don't mean just contraception but with devices, with drugs and so on. A good example is the MOD database which the FDA has. That is strictly voluntary for devices, and so on. So, you never know the denominator. All you know are the events or the numerator. The only way that I could see that you could do this systematically is that in some way either the companies or somebody has to be required to do it. In other words, if it is just left up to say, well, if somebody is maybe going to do the study we may never-ever get the data. Do you have any suggestions this morning?

DR. PETITTI: Well, I think that the

problem of not having good postmarketing data about safety is not limited to the hormonal contraceptive arena.

DR. SCOTT: Right.

DR. PETITTI: I think what we can say about hormonal contraceptives and what makes it easier to want to do a postmarketing study, both for the sponsors and for the FDA, is that we can reliably anticipate what kinds of safety events will be of interest, and we can reliably anticipate that we will have spontaneous reports of the worst things that happen--you know, the first set of the worst things that happen.

I think from the sponsors point of view, they should recognize that this is going to have a huge impact on their product and on the public's acceptance of their product. And, we know how to do these studies. We know what to look for and we know what the consequences are of not doing this kind of study.

So, I think we can, perhaps as a committee, make some recommendations to the FDA

that they should more strongly encourage the conduct of this kind of postmarketing study, offer some acceptable designs. I think ultimately the incentives have to be for the product developer to avoid the catastrophes that we have seen for some of the other newly marketed products.

DR. SCOTT: So, your recommendation is that the product developer do the studies? The FDA says they won't requireB-

DR. PETITTI: Well, I don't think NIH shouldB-well, NIH is not a source. If it is not the industry, they won't be done.

DR. SCOTT: That is right. No, I don't think they will.

DR. PETITTI: Yes, I mean, they are sending in an RO1 application to do a study that I described is a waste of paper.

DR. LOCKWOOD: Dr. Gilliam?

DR. GILLIAM: Actually, you just touched on my point, which is that of funding. I think the current system makes it a complete disincentive for a company to do this type of study. Instead, many

studies are more likely to deal with issues of additional indications that might help to improve the marketability of a drug. So, I wanted to get your thoughts on funding and why people would do this and other potential sources.

DR. PETITTI: Right now there is no public source of funding that is likely to be worth the effort. NICHD, as we heard, which is the logical source of funding, simply is under-funded to do this kind of study. There are other priorities that I think reasonably take precedence over determining whether or not a new product is as good as old products. That proof should be in the interest of the company.

DR. LOCKWOOD: Dr. Stadel?

DR. STADEL: Thank you. I would like to offer a couple of comments. I have done a lot of Phase 4 work in my time at FDA and want to reflect on a couple of things.

One is the question I think it is really a beautiful description and coverage of the issues, and the approach Dr. Petitti talks about for being

able to look at an issue if it comes up, would be great. The question is who supports the standing framework. There is generally, at least in my experience, a product-specific Phase 4 commitment that usually required some sort of signal, either pre-approval or post-approval; that is, there was an issue that negotiated a Phase 4 approach that was product specific.

Now, one could argue that any new contraceptive needs this kind of thing. But it is not quite the same. There is usually a tangible safety issue, that is something a little different about this product that either came up in the Phase 3 testing or that emerged from the alarm system, which does produce a lot of problems but it won't go away.

So, I have seen one kind of issue that was product specific where we identified the issue. We entertained a company proposal. We used epidemiologic review within the agency. There is a group and they can draw on outside reviewers also. Then, ultimately, the division negotiated with the

company for a product-specific Phase 4 study.

I think it is most unfortunate that there are not funds available to establish an ongoing cohort and nested case-control resource because I think actually the cost of that these days, relative to the cost of setting up a cohort study years ago, is actually quite modest. That is the per unit cost. And I hope some day that will become available. But I think there is a question of how much one would ask an individual company to support that. I think there is a difficult issue here and I don't know any way to get away from that.

A couple of other minor comments, I do think case-control studies have been useful for effects of current use. That is, the early studies of vascular disease were really effects of current use, although it has been heavily used for the effects of long-term past use in issues like breast cancer. It also is useful for current use. That is just a minor comment.

I think there may be sometimes roles for

large simple trials. Again, it would depend on the issue. We talked a lot about comparative efficacy evaluation and the problems of sample size if the pregnancy is the outcome. I have seen in one caseB-I don't know the details of it, but I have seen that a large simple, open-label trial measures both the drug and how it is marketed, and there is actually some value to measuring how something is sold in addition to what is sold.

So, an argument could be made that someone might propose a large simple, open-label trial to say we want to look at how we sell our product relative to how other products are out there the bottom line of effectiveness considering both the chemical and how we deliver it. So, I wouldn't rule that out but it is really not my main point. I think my main point has to do with the issue of product specific versus general surveillance.

Thank you.

DR. LOCKWOOD: I am going to get to you, Dr. Tobert, in a second. I think that this raises a very important issue, which is that we really

would be, I think, setting up an unfair barrier potentially to the access to new hormonal contraceptive agents and creating a sort of an unfair additional set of costs on new sponsors, or sponsors bringing new agents, when we haven't had this potential regulatory burden applied to previous agents. We are discussing it precisely in the context that relatively safer agents are being offered, presumed safer because they have lower levels of estrogen, that have at least reasonably comparable efficacy. I think it is very clear that very low-dose contraceptives, if used appropriately, even reasonably appropriately, have comparable efficacy. I think the issues obviously with BMI, missed pills and so forth.

So, is it fair to recommend that there be obligatory Phase 4 commitments to obtain safety data when there is no reason a priori to suspect that a given agent would, in fact, incur a higher risk? So, this is sort of a philosophical question more than a technical one. Does it create an unfair burden? And, what circumstances might there

be where it would seem to be the appropriate thing to do?

Now, having said all that, it seems to me that some manufacturers would want to do it in order to provide additional indications; that they have completed a very carefully done Phase 4 trial along the lines that have been described, that, clearly, this agent is associated with lower rates of venous thrombotic events compared to another and, therefore, we are going to go back and ask for this as an additional indication to be used in settings where there may be an increased risk of venous thrombotic events.

So, I would like the committee to think about that and to comment on it. It will lead into the set of questions that we are going to have to deal with in a minute. Dr. Tobert?

DR. TOBERT: Yes, I thought it was a very nice presentation, Dr. Petitti, but I think maybe you are a little quick to dismiss the randomized, controlled trials. I think you did so on the basis of cost and practicability more than any scientific

reason. But I do think there may under certain circumstances be a place. I mean, after all, all epidemiological studies, no matter how well done, are always subject bias and confounding. It can be minimized but it can never be totally eliminated, and there have been many cases where randomized trials have produced results that are completely different from what the epidemiology suggested, and we are all aware of those.

So, I do thinkB-and this takes up Dr. Lockwood's pointB-that if a sponsor wishes to claim that their product, whether it be a very low estrogen product or something else, has a lower risk of VTE or other vascular events, in order to be able to make that statement in the labeling, that they should be required to do a randomized, controlled trial.

I think if you have a good reason that your product is safer it would be ethical to do in high-risk women, older, more obese, and so on. I think it would be practical because most of these events occur fairly quickly. And, I just think.

unless you have very big hazard ratios, that any epidemiological study is not that reliable. If it has a hazard ratio of 5 times, fine. But more typically you get 1.3, 1.4 and so on and personally I always find that is hard to interpret.

I would further make the point that the most visible drug withdrawn in recent years has been Vioxx and that did not come about primarily through epidemiological research; it came about through a randomized, controlled trial.

DR. PETITTI: I think when I was thinking of Phase 4 that I was not including studies that might be done in order to claim an indication. I think that any company or product that claims that their hormonal method of contraception decreases or is safer in terms of venous thromboembolism would have to have a design that proved that, and you would not permit that claim in the absence of empiric data of high quality that proved that claim and, clearly, the randomized trial would be the best way to do it, although I believe that we should be open to the possibility that a well done

non-randomized study would permit that claim.

But I don't think that the primary way to determine whether or not the product is sort of the same as everything that is already there is a randomized trial. So, I just wanted to make sure that we understand the difference between Phase 4 studies done for a new indication versus Phase 4 studies in order to evaluate safety.

DR. LOCKWOOD: Diana can respond to each of the questions if it is specifically addressed to her. Dr. Peterson, Berenson and Stadel?

DR. PETERSON: I think this discussion is really getting at the heart of some important issues. One starts with the background that Diana mentioned yesterday, that we know more about the safety of oral contraceptives than any other drug in the pharmacopeia. So, even though we still have some important questions, we are starting with an enormous body of evidence about the safety of oral contraceptives.

The question then about new products that we focused on in the last little bit is this issue

of uncommon but serious adverse health effects and the extent to which there is a collective responsibility to identify those, whoever's responsibility it ultimately turns out to be, and whether or not we can afford it. I think the outline of the methodology is right on target. These are clearly going to be expensive studies. There are ways to try and make them less expensive but they are still going to be expensive and ultimately somebody is going to have to decide do those studies get done.

The other issue that really I think permeated all the discussion yesterday and came back up again today in the public comment is this issue of the primary purpose of the oral contraceptive to prevent pregnancy.

Then the question comes up is there responsibility collectively to determine, within relative precision, how effective the products are? If we accept that there is a collective responsibility to do that, then we say, well, is it for the whole group or, as has been suggested a

number of times, is it for key subgroups including women who are obese, whatever?

So, if we say, well, there is that collective responsibility at least for the entire group of women who might be using thisB-let's stop short of subgroups for now because that complicates it-Bthen have we achieved that in our strategy to date? I would suggest not in terms of what we decided yesterday with premarket approval because James tried to help us with a point about the delta to say, well, if we accept a relatively wide delta, then we potentially don't answer Dr. Monroe's question yesterday.

Dr. Monroe said, well, we are looking at these new products relative not to non-use of contraception but to a class of highly effective steroid hormonal contraceptives. If that is the benchmark, then we say, well, it is one or two percent pregnancy rates.

Then we would have to say, well, with the comparative active control trials that we recommended for premarket approval, if there is a

delta that says, well, you know, it might be 4 percent, 5 percent but we will accept that for premarket approval. But there is some sort of duty owed later on to get a more precise estimate.

The problem comes with a slippery slope where, if you get a product that, let's say, is 20 mcg with a different formulation and it is 4 or 5 percent, the delta accepting that, and then you get a 10 mcg product and you have another delta of 4 or 5. Then you can get to 9 or 10 percent and you are on a slippery slope that at some point falls out of a reasonable person's range of is it still in that class of highly effective steroid hormonal contraceptives.

So, based on everything that was said yesterday and today, it seems like there is a fair consensus that there is a collective responsibility to consumers and providers to develop a reasonably precise estimate of effectiveness at a minimum for the general population and ideally for subgroups.

So, I think that we are going to have to wrestle with this issue of uncommon but serious

adverse health effects, and whether anybody can afford to pay for those, who should it be and how does it get done versus the effectiveness issue. I think there is a general sense that there is a responsibility and that we ought to have a strategy for how that responsibility is executed.

DR. LOCKWOOD: Yes. I mean, it is sort of ironic that, in fact, there is almost less need for safety studies and more need for Phase 4 efficacy studies with newer lower-dose formulations. It is like 10, 20 years out of sync.

But one simple expedient might be to say that, in the approval trial, we have accepted a much wider interval for non-inferiority, for example, and when it crosses a threshold that we are uncomfortable with, and we need to define what that is, that might be a trigger to warrant a Phase 4 efficacy study in the real world and we will be able to then document with much more precision where in that interval reality is. Dr. Berenson?

DR. BERENSON: I would like to comment on the statement that the NIH does not fund these

types of studies. They have funded--NICHD is funding these types of studies, although they should be funded at a much greater degree. They are currently funding four RO1s examining the relationship between injectable contraception and bone density. That is where all the data on this has come from.

The cost of these studies is very high. I am the PI of one of them. We have spent over three million dollars during a five-year study that followed 700 women initially, of which 350 stayed in the trial for two years. That is a very high follow-up rate compared to the general population's use of contraception.

If you start generalizing it to all women--and of course we tried to recruit all women but the types of people that respond to clinical trials often are not reflective of the general population and stay in at a higher levelB-you are going to have a much lower follow-up rate. We have had problems with disconnected phones and frequent moving.

Now people have cell phones. They use these temporary cards. They are only good for a month and then their cell phone number changes. So, even though you think people are more accessible now, they are actually becoming more difficult to contact.

I don't know if it will be an advisable idea to place this burden on the manufacturer. Again, I get concerned as to whether or not they will consider it worth their while to market these drugs at all if the burden is so high that they can no longer make a profit on it.

With regards to the computer-records research, that is certainly an excellent idea. There are many ideas you put up there that give us food for thought. But women that fill a prescription at the pharmacy for their contraception cannot be contacted blindly later on by a researcher unless she has consented to this in advance in most institutions.

At Kaiser, where they are your own patients, you can probably do this but I,

personally, wouldn't want to receive a call from someone I have never met to tell me that they found out from the pharmacy what kind of contraceptive I received and they have some questions about whether or not I received an abortion, or took my pills, or other such personal questions.

Without that patient contact, it is very difficult to know if the patient ever took the medication. All you know is that she filled it at the pharmacy, and I agree, you can't get the pregnancy rates.

So, you really cannot get good data on this without prospective, controlled studies. One of the things this committee could do is make a strong statement that there need to be more of these studies funded by the NIH. There is certainly a number of applications that come to them trying to do this.

DR. LOCKWOOD: Just to put things in perspective, the NICHD, which theoretically funds all research for pediatric, women's health, women's reproductive health, obstetrics, gynecology, etc.,

representing about 80 percent of the population, 70, 68 percent of the population, receives less than 5 percent of the NIH budget and its relative proportion of the NIH budget has continued to shrink over the past 20 years. You know, the thing speaks for itself. Dr. Stadel?

DR. STADEL: I would like to comment briefly on the potential for randomized trials for safety issues in Phase 4. I think the standard of evidence that has generally been accepted in my experience is that, for efficacy, an experiment is required, a trial. For safety issues decisions are made on observational data. And, I think that is a very important distinction between what is required to market an intervention in terms of the public interest versus what the level of evidence is needed to make a safety decision.

Historically, the decisions about dosage in oral contraceptives and cardiovascular disease were made on the basis of observational data and we are where we are on the basis of observational data. So, I think it is very important that while

someone wanted to do a randomized trial on a safety issue, which would be fine with me, that that not become the standard of evidence unless you do a randomized trial. I think that is a very important issue that needs to be kept in mind. Thank you.

DR. LOCKWOOD: I think it defies imagination, the cost of a study, a randomized clinical trial, to look at the preferential occurrence of venous thromboembolic events with two different agents. It would be the NICHD's budget for example.

We are going to move on to the specific questions now. We are asked to address what designs should be considered for Phase 4 studies of hormonal contraceptives and what are the strengths and limitations of each type of design. We certainly heard quite a bit about this. What are the most important cost/benefit considerations and limitations of each design, for example, a more rigorous design but a delay in obtaining outcome data, cost and so forth?

Diana, do you want to make a sweeping

summary statement?

DR. PETITTI: I think we have to make some statement separately for effectiveness, for safety and for new indications. For a new indication, I believe that a claim that their oral contraceptive is safer in terms of venous thromboembolism as a labeling claim should be subject to the same standards as any other labeling claim. It could include, for oral contraceptives, very well done observational studies and RCT. The RCT has the advantages of being more definitive but it is incredibly costly, and the problem with an observational study is that, no matter what you do, you have residual concern that you haven't actually measured what you want.

For use-effectiveness postmarketing, I think these should be prospective studies involving representative populations with active follow-up involving direct contact.

For postmarketing studies to look generally at. is this risk of venous thromboembolism bigger or smaller than a bread box,

which is what I think we do with most of our safety studies of venous thromboembolism, I believe that the design I laid out is feasible in settings other than Kaiser Permanente and that that is the ideal design.

I do think that we should not presume that we can judge what every IRB in the country would say about contacting women in order to gather this information because sometimes you can go directly through the physician. You go from the pharmacy to the prescribing physician to the patient. So, I think we need to leave open and identify the ideal design. I believe that database studies in the absence of direct patient contact have the potential to be highly misleading and should be discouraged.

DR. LOCKWOOD: I don't think anyone would dispute that, and I think there is consensus in the group regarding the first specific statement that, for a new indication of safety, a randomized clinical trial probably is not doable, but a very carefully done, well-constructed observational

study is appropriate.

For effectiveness, a description of a prospective sort of observational trial to really clarify where, in that interval, efficacy rests-BI think there is consensus on that one as well.

The third point, in terms of sort of bread-basket safety, unless the statisticians want to get into a discussion about the specifics you have laid out, I think the philosophical question we need to wrestle with is should that be obligatory. Dr. Johnson is going to tell us.

DR. JOHNSON: Actually, I was going to ask that question because if we make this that you can look at this or you can't look at this, then the other question is how is it funded. I can't quite imagine that a pharmaceutical company would want to pay for something that is going to be very costly that may make their product look worse. So, are we going to be able to really get this?

I mean, I would really like to see long-term data on VTE risk or any thrombosis risk, be it arterial or venous, in patients using

contraceptives because there clearly would be an advantage of one that had lower risk, and to select populations especially. But how are we going to get there? Can we require this of the pharmaceutical company? If not, then how are we going to have good information on the safety of new products?

DR. LOCKWOOD: Dr. Gillen, Tobert, Scott and Stadel.

DR. GILLEN: First, I just wanted to say that I think Diana's points are excellent and I really appreciate the design strategy of the nested case control and the cohort study to kind of achieve a couple of goals.

I really wanted to speak to Dr. Lockwood's first statement, and I think the point is very well taken. You know, is this really an undue burden given that we are talking about a relatively safe group of interventions here. I think the flip side of that though is that our concern is public health in general and we are talking about also a widespread use of interventions here.

So, even though we are talking about rare events and we are talking about relatively small risk differences, the public health impact can be quite large. Although I wouldn't go to the standpoint of saying that we should be doing Phase 4 randomized trials because I think they are, you know in our wildest dreams, somewhat inconceivable logistically, I do think that fairly well organized surveillance systems for safety that are actually proactive in maintaining cohorts in an observational fashion, even given all of the drawbacks that we know about and potential unadjustment for confounders and things that are going to occur in observational studies, it is still definitely something that is called for in such a widespread use intervention.

DR. TOBERT: I actually would just like to comment on this cost issue. I mean, these trials, these large randomized trials, if they are done using the large, simple trial concept where you eliminate the collection of all data but the most essential, they can actually be done quite cost

effectively. Very large trials that I have been involved in recently have been costing on the order of about $1,000 per patient per year. I mean, that is not so huge.

But I do think that if you are trying to show or refute a hazard ratio that may only be 0.7 or 1.3, which I think is what you would expect if you have, say, a low estrogen pill, I think you cannot reliably determine that except through randomized trials. That is not to say there is never a place for observational studies. I just think that where the effect is not big, then the results are not sufficiently reliable.

DR. LOCKWOOD: Dr. Scott?

DR. SCOTT: Yes, I wanted to get back to what Bert said about collective responsibility to collect these data. I still am not quite sure who would do it, or how, or who would pay for it. Is there a way, for example, with any prospective, randomized trials that at least those data could be followed long-term and collected in a database and at least be saved? Or is there a possibility that

even some of the organizations or societies that have an interest in women's health could help with these studies too?

But I don't see any motivation for a company to do it, and I don't see any funding any place to do it. So, from a very practical standpoint, even though we all agree that this would be desirable, how can it be accomplished?

DR. LOCKWOOD: Dr. Stadel?

DR. STADEL: Well, historically the collective issues have been addressed with public funding. I was involved in doing that for many years with the NICHD and I understand the budgetary problems. But I think there is still an issue here of what is a public responsibility and what is a private responsibility. Big studies on oral contraceptives and risk of breast and ovarian cancer were set up with government funds, big studies of cardiovascular disease, prospective studies in the U.S., the U.K. and so forth. Those were collective responsibilities.

There are a couple of other comments I

would like to offer on what is going on here. I don't see how, if I were back in the FDA, I could justify trying to require a company to do a Phase 4 study to show that their product was safer. If they wanted to, that would be fine but I would not attempt to justify asking them to do it.

I do think Dr. Tobert raises a good point about associations that are less than twofold and the experience in observational studies as being mixed with weak associations. There is also an important legal distinction about association that is twofold or larger as opposed to smaller. So, there is an area there where some things may not be completely resolvable. You may never get complete resolution about whether the risk of VTE is 20-30 percent different between one OC formulation and another. I really doubt that those are resolvable issues because I would want to comment that one big difference between trial and observation is that the trial is an intervention and it sometimes changes the outcome.

I have dealt with some safety issues where

findings in randomized trials and findings in observational studies were different and ultimately an explanation was found. One that comes to mind is bisphosphonate and GI bleeding where there was no association in the trials where women were very carefully taught to stand up take the bisphosphonate correctly. Findings did occur in Phase 4 and they were not due to bias, they were due to differences in how the drug was used. So, there is a different role at times but it is an important role because a safety finding is still a question of how well can people use something safely and not just in a trial.

DR. LOCKWOOD: Dr. Gilliam?

DR. GILLIAM: I wanted to respond to the comment about what is the most important and appropriate point to get efficacy data as well as effectiveness data. While I think much of that will come from Phase 3 and Phase 4, in the particular case of women with higher BMIs I think it is really important to start moving that forward so that we have dosing and efficacy studies in

Phase 2 in obese women. I think that would be the most efficient, probably needing to use surrogate endpoints looking at PK levels. But I think that would be the most efficient way to study those particular women and not wait till later phases of testing.

DR. LOCKWOOD: I hope that you got the sense of the committee in our discussions yesterday that not only do we recommend or suggest that there be much more broad entry criteria for future trials for approval, but that there be analyses of women with high BMI using surrogates-Bovulation and so forth-Bto sort of buttress the indication trials and also to give us a little better sense of whether this would work in the extremes of BMI. I think we nailed that yesterday.

DR. TRUSSELL: I dissent from that. I do not believe in surrogate endpoints, certainly not ovulation for a contraceptive because there are many other mechanisms of action.

DR. LOCKWOOD: No consensus on that.

DR. GILLIAM: No, I am talking about dosing

studies in Phase 2 trials for BMI so we have some sense in obese women how these work so that they are included in that phase of the study, and not necessarily excluded from Phase 3.

DR. LOCKWOOD: Dr. Monroe?

DR. MONROE: Yes, I have been writing a long list of questions and comments. Let's talk a little bit about Phase 4 studies in general. I have heard a lot of comments where it appears that certainly the majority of the people feel that there is no incentive for the sponsor or the company to do them. And, that is not always the case. As a matter of fact, we have requested or recommended to some sponsors that they do that and they have agreed to do that. So, the precedent has already been set where we have asked sponsors to do Phase 4 studies and they have agreed to do that of a large nature and not gone into the designs.

What our ability is to coerce or demandB-that is a different thing but it is a negotiation process, and if it looks like it is a win for everybody, it is a doable entity and

sponsors will do it. It depends really on a particular product that one is reviewing.

If it has a de novo progestin, as an example and, as Dr. Petitti said, we don't necessarily know whether this progestin is going to be similar or very different, or whatever, sometimes the company recognizes that it is in everybody's best interest to have those kinds of data.

As Dr. Petitti also said, sometimes we know that bad things are going to happen and if they happen shortly after the release of a product this could have a big impact on the acceptability, and so on. So, sometimes it is advantageous to have such data in hand, to have such studies in place so that you can address these concerns.

So, the issue of fundability I don't think is an insurmountable obstacle, and it is actually why we didn't ask you the question should they be done because we have certain feelings that in certain cases we think that they have clearly a place.

So, you notice there wasn't such a question because there have been instances where we thought it would be useful. Then, there have been other instances where, because of certain things that have occurred post-approval, one has to go into the kinds of databases that, again, Dr. Petitti has made reference to, and sometimes it is nice to have this all prepared ahead of time.

So, again, there are incentives for the sponsor, the company actually to want to do this because there are merits. So, in those cases funding is clear. So, that is just sort of a general comment.

I don't know whether you want to break the train of thought or not, but it goes back to something Dr. Peterson said about the concept really of looking at effectiveness or efficacy in Phase 4, which is not something I think we have traditionally done. At least from the agency's point of view we have focused more on safety. You raised a couple of concepts. May I explore those now or would you prefer to defer those because they

don't relate to the feasibility so much?

DR. LOCKWOOD: No, please.

DR. MONROE: you had mentioned that perhaps approval could be based, again if one is using this concept of this non-inferiority design-Band, correct me if I misrepresent anything you said-Bwith a certain wide interval. Then, having met whatever this comfort level, this comfort interval, is, go and do a Phase 4 study perhaps to more precisely define it. I think I am capturing your thoughts correctly.

In regard to that, I would just like to ask you two questions. You said as long as it is within this level of comfort we have for this comparative studyB-do you have a level of comfort that you would like to at least share with me or the other members of the committee or are you going to leave that up to the agency to decide what its level of comfort is?

I would actually like to get some feel from you about what your level of comfort would be. I know what mine is but it may not be the same as

that of my three colleagues to the left or my colleagues to the right. I can ask them any day, but I would like to hear your levels and perhaps anyone else who would like to share that with us.

Then, as a follow-up on that, depending on what the Phase 4 study shows, and we won't get into design issues because that is another level of complexity, would you then be comfortable just defining in the label whatever that is so that the healthcare provider and the consumer knows what it is? Or, what if it comes out near the level you had discomfort with because once a drug is approved it is very hard to do anything with it? So, I would just like to carry those thoughts through and maybe we could get some feedback either now or if you would like to table that for this afternoon because it may be somewhat aside.

DR. LOCKWOOD: No, I think this is an opportune time. And, why don't we discuss it. We will talk about the difference between our comfort with point estimates versus interval estimates.

DR. PETERSON: It is a key issue and, you

know, there was actually a question yesterday from a committee member about the graphical representation of failure rates, which is intended to improve communication to consumers. Then the question was, well, how do you decide how many categories to have? How do you decide typical and perfect? I think the bottom line to that is trying to decide what is meaningful.

A group of highly motivated, highly informed people debated that and I think it is going to be difficult to achieve consensus about what is truly meaningful because we worked, as James said, for months and had a lot of debate about whether to have four strata-Bwell, that is defining what is meaningful. If you put everything in that same category you are saying, well, what is meaningful is the difference between that first row and the second row, and the second row versus the third row. So, I think that that is one of two very difficult tasks, is to decide what is meaningful.

You said yesterday, when you were talking

about the body of information we have about the class of drugs, that we are probably at 98 or 99 percent and would it be a meaningful difference if a lower-dose pill was at 95 percent. And, I think that is the question you are asking us and I think, you know, each of us will have our sense about that.

The other point that we are discussing is the truth about that meaningful difference as best we can estimate it from a measure or a sample. That then gets into this issue of how confident we are that we have hit the mark in making that assessment.

Those two are inter-related because if you say, well, a meaningful difference is somewhere between 1 percent and 10 percent but within that range it is okay, then you can design a study that gives you a reasonable level of certainty that it is within that range. If that is fine, then that is fine. It actually simplifies a lot of things.

But if you say there is a meaningful difference between this class of steroid hormone

contraceptives that is in the 1-3, 1-4 percent range but if it is in the 7-10 percent range that is really meaningfully different, then that needs to be clear and explicit and then the studies need to be designed to give you the ability to distinguish between those two meaningfully different groups.

So, it is not the answer to the question but it is what a lot of people have been struggling with in trying to communicate this concept of effectiveness with the WHO consensus guidelines.

DR. LOCKWOOD: Do you want a number or are you satisfied with that general response? I feel like one of those talking-head hosts.

DR. MONROE: It would certainly be helpful to see if what you have just conveyed is sort of the opinion of all your peers here because this is a difficult concept we, within the division, have. Just like you said, you have had many discussions, we have had many discussions. And, if you could give us sort of a sense of where this meaningfulness kicks into place and also, again,

help us a little bit more because a lot of the things we are talking about are just point estimates.

We know that these point estimates have degrees of uncertainty associated with them based on the 95 percent confidence intervals. Are we talking about the whole range? Are we talking about the point estimate? Because in the best circumstances, based on the confidence interval we are probably going to add another percent or another 1.5 percent depending upon the sample size of the trials, and so on.

I know these are perhaps difficult questions. They are philosophical questions in a way because they don't have real simple answers, but anything you could do to help enlighten us as to what you folks think about this concept would be very helpful to us.

DR. LOCKWOOD: We are going to put ourselves on the spot and we are going to answer question 15a, which is, is there a pregnancy rate that would be unacceptably high? We are going to

define that both in terms of point estimates and intervals, and then we are going to modify whatever statement we want to make and we are going to go around the table to do that. Dr. Johnson?

DR. JOHNSON: You want just a hard number, a percent? Correct?

DR. LOCKWOOD: A point estimate deviation. Assume 1 for benchmark Pearl Index since we have to have a simple way of doing this, and then a confidence interval beyond which you would be uncomfortable having the agent approved, and a second threshold where you would like to see confirmatory Phase 4 efficacy quantification studies.

DR. JOHNSON: Say the second part again.

DR. LOCKWOOD: So, it is sort of three questions, point estimate beyond which you are uncomfortable having an agent approved; two, an upper bound beyond which you are uncomfortable having an agent approved; and, three, an upper bound where you really would insist on a Phase 4 study to further quantify the exact interval.

DR. KAMMERMAN: Lisa Kammerman. I just wanted to give a little context from a statistician's viewpoint that maybe would help. Historically, the division has looked at the point estimate of the Pearl and compared that to "historical" values of the Pearl, 1.5, 2.0. So, part of this question is asking do we want to compare point estimates and what is the limit--if we choose a point estimate, what is the choice of that point estimate? So, that is really where the point estimates come in.

But I also want to add that we are also interested in that delta. How much is that non-inferiority margin going to be? But I also want to submit that I think we have already been using the delta a little bit without thinking of it that way because when we get the Pearl Index we have a confidence interval around it.

So, even though the point estimate I know for a recent trial was around 2, the confidence interval went up to 6. So, with 95 percent confidence we can say that the true Pearl Index

could have been as low or high, depending on your perspective, as 6. So, in some sense, we have already been using a non-inferiority margin of 4.

So, if we look at a difference between a new treatment and an active control and we come up with a difference, say, of 2 and now we form a confidence interval, we are willing to say that we are 95 percent confident-Bthis is an example, that the new product perhaps could be, with 95 percent confidence, 4 points or 2 points worse than the known product. So, that is a little bit about this Pearl Index and deltas. I hope that helps.

DR. LOCKWOOD: Okay, we are going to do it my way, but now you have some numbers dancing in your head that will help you a little bit. Dr. Johnson?

DR. JOHNSON: I am actually comfortable with what you are currently using. I know it is sort of cheap of me just to grab that but, I mean, to have the number be 2 percentB-I was going to say 2-3 but that is hedging a bit, and have it be, I was going to say, within a confidence interval with

the upper level being 5, but it sounds like you are already at 6. I mean, I think accepting that we are willing to approve or willing to have you approve a contraceptive that has a little bit lower effectiveness is reasonable as long as patients are well informed. I would think that any confidence interval that exceeds 5 or 6 certainly needs to have a Phase 4 trial.

DR. LOCKWOOD: You get one number so 2, 5 and 5 or 2, 6 and 6?

DR. JOHNSON: I was going to say 2, 5 and 5 so I will stick with that.

DR. LOCKWOOD: Okay. Dr. Stadel?

DR. STADEL: I decline to answer with a number. I feel this is something that is more appropriate for opinion of those who are closer to the clinical fire than I am. I would only say that I--I talked earlier about thinking that--I have heard people express the view that failure rates substantially higher than I might personally be comfortable with are acceptable to them.

I would really say I defer judgment here

to peopleB-this is an issue where I really want to know what women who are using the products think. The possibility of categories of products that are labeled according to how firm their evidence is about effectiveness I think might be appropriate. But ultimately I think this is a decision that lies within the agency after they consider all of the information and, hopefully, the input from women about what they want to buy.

Thank you.

DR. LOCKWOOD: We have been asked to provide numerical guidance. I don't think we can be more blunt about this. So, you can abstain, and that is perfectly acceptable, or give me the numbers. Dr. Petitti?

DR. PETITTI: Well, I am going to directly answer the question here which presumes a historically controlled trial, and use the numbers that were given by the statistician and say that, for historically controlled, trials 2, 6, 6. Now, I am also going to give you a delta for an active trial. My delta for an active trial is 3.

DR. LOCKWOOD: So, 3, 3?

DR. PETITTI: No, you only have to give the delta. Right? You only have to give the delta, which is the amount of difference compared with the standard product you are willing to accept in order to approve the product. Actually, I should be consistent. My delta should be 4.

DR. LOCKWOOD: Tell me the difference between the delta and the upper bound--

DR. PETITTI: The delta isB-you tell him!

DR. GILLEN: The delta corresponds to the upper bound of the confidence interval for the difference that you are talking about. That is what you are rejecting.

DR. MONROE: Dr. Lockwood, I hate to interrupt but I just want to get one bit of clarification. When you have points and upper bounds, obviously they are inter-related but independent. So, if you are doing a large study, you are going to presumably have a smaller delta because here it is a simple event, it either occurs or doesn't occur. So, again, and we will ask Dr.

Gillen and our statistician or anyone else who wants to comment on that, let's say in actuality you wind up with a point estimate of 4 but your delta is still under your 5.

I know I am making this very complicated because in the real world that it going to happen a lot. I think a lot of our trials will be like that. In, say, Dr. Johnson's presentation, do you have to meet them all or as long as you meet one of the two? I would just like that bit of clarification.

DR. LOCKWOOD: I hope everybody understood the way I worded this. I want the calculation of a point estimate, based on the Pearl Index, beyond what you will be uncomfortable approving the agent, and the upper 95th percentile of that estimate beyond which you would be uncomfortable approving the agent, and the upper limit that you would want an additional study to confirm in a more precise way in a Phase 4 setting what the actual number is likely to be.

DR. MONROE: Do you understand the question

because I think in many trials we don't have a gap of 4 units from the point estimate and the upper bound. We may in a very small trial but I think in the larger trials it is usually tighter than that. Then Dr. Slaughter will ask a question right after Dr. Gillen answers.

DR. LOCKWOOD: I think the reason that it is wider is that we are assuming, based on yesterday's discussions, that this is going to be a far more inclusive trial with a far more heterogeneous population which assumes higher rates of non-compliance, potential actual user method failure because of a variety of circumstances that are not normally present in currently conducted trials.

DR. MONROE: That is not going to affect the variance, I don't believe, because you either are pregnant or not. It is not like a continuous endpoint where you have a very broad scale. So, again, would you clarify that for everybody, please?

DR. GILLEN: Yes. I think that, for a

second, we have to get away from the point estimates and think about variability here for a second. We have to put ourselves into a decision theoretic point of view. The question is what is the hypothesis that we are rejecting when we do one of these non-inferiority trials.

Let me just finish quickly because there is a lot of confusion about what a point estimate relates to a confidence interval and how we are thinking about this.

From the non-inferiority perspective, let me just say that the hypothesis that we are rejecting is that we are no worse than delta away from the active control. Okay? That corresponds to the upper bound of the confidence interval. That is what is defining that delta. So, you are thinking about worse-case scenarios. What are the hypotheses that you are ruling out versus the active control?

Point estimates always correspond to variability. So, if we are just quoting point estimates, everybody is missing the variability

part of this. We need to be thinking decision theoretics, what are we ruling out in terms of hypotheses and alternatives.

If you are going back to the historical control trial what you are assuming is that you have a benchmark so that you have a point estimate now for some sort of comparison group which has zero variability. Okay? So, that is what we have to be thinking.

So that is why we are also considering the impact of the sample size here because we now have two variable estimates that we are comparing. What do we gain for that? Well, we gain the comparability between the groups because we know that there is not zero variability in the historical control benchmark that we are making. We also know that we don't necessarily have comparability with respect to all the other covariates.

So, I am hoping I am making that clear. When we are thinking about point estimates we really need to be thinking about the hypothesis

that we are rejecting. That is what we have to be considering here, and what is the worst-case scenario.

DR. MONROE: So, we really have two questions because I would like to know, again going back to the way we have been looking at drugs in the past where there have been non-active controls. We have a point and we have an upper bound and that upper bound relative to the point estimate is really driven just by sample size, and that is the way another guidance is written here, the EMEA. They said that they want the upper bound within roughly one percent of the point estimate and that is really a sample size. You have to accumulate enough events to define that.

So, I just want everyone to understand. So, there is an uncertainty. Again a relative point estimate. The upper bound helps to define it. That is in the historical controls. Then we have the comparator to the active control and there is another degree of uncertainty, and I am going to defer to Dr. Slaughter who is going to clarify this

concept that I can't.

DR. SLAUGHTER: Well, I just wanted to make sure that we weren't confusing the two, particularly when we are talking about active control trials where we are talking about a 95 percent confidence interval around the difference between the drug of interest and the comparator. What we are interested in is the delta, how much worse can the drug of interest be than the comparator and what is the acceptability, what is that delta. That is what we are interested in getting in terms of a comparative trial.

Further, if I might, in this discussion I would like to talk about what Dr. Peterson termed the slippery slope, or as we have been internally discussing it as drift in efficacy, when we talk about this delta and the confidence interval. In other words, the next drug compares to the drug that was worse and it gets worse and worse, and what is the acceptability and trigger there?

DR. LOCKWOOD: Well, that may well represent another question so let's just continue.

You don't have to give your point estimate. You can just give the delta and assume, if you want to do both historical and active, but I think active control trials is what we are really interested in.

DR. PETITTI: Yes, I wanted to clarify that to be consistent with what the FDA has been doing--appears to have been doing--my delta is 4.

DR. MONROE: Dr. Petitti, I don't think that we can say that the FDA has been doing that. That was a particular example so we can't construe that and generalize it.

DR. PETITTI: I think a delta of 4 is a reasonable amount of lesser efficacy to accept in a comparative trial.

DR. LOCKWOOD: Just to be very specificB-

DR. TRUSSELL: She has answered it. It is 4.

DR. LOCKWOOD: But I want to understand what we are talking about because some of us are obstetricians, not statisticians. If the benchmark that you are comparing it to has a point estimate of 2, 2 pregnancies per 100 pregnant women years,

you would accept 6 as the upper 90--okay. Let's go on. Dr. Gilliam?

DR. GILLIAM: I am fine with those numbers, 2, 4 and 6. I think it is reasonable with very similar products.

DR. LOCKWOOD: I am assuming you would use the same number to mandate, indicate or suggest or recommend, or whatever language you want to use, a Phase 4 efficacy assessment? Or, would that be a different number?

DR. GILLIAM: No, that is fine. The only thing I want to add is that these are guidelines so that if a company could argue that the numbers become too outrageous for the study to be feasible, I would want the company to be able to say, or the sponsor could have an opportunity to say whether they need a different type of study design or a different number that they thought was reasonable based on potential user compliance issues.

DR. LOCKWOOD: And I am sure that is assumed in the negotiations that go on during the approval process. Dr. Hillard?

DR. HILLARD: I am going to abstain from giving a number. I need to say that I am looking at all of this and thinking about this in the context of not feeling comfortable about comparability and generalizability and applicability of the numbers that we are looking at so far. We have talked about the fact that we don't know about women of weight.

We don't know about younger women. So, I think that to say a priori that we know what we are comparing is problematic as far as I am concerned. I am also looking at the fact that we have a typical user failure rate of 8 percent and, therefore, we are accepting that for our current pills as well. So, I am not going to give you a number but I am very concerned about comparing apples and oranges.

DR. LOCKWOOD: Again, we are not asking people to violate their conscience but we have been asked--

DR. MONROE: I think that is an acceptable option. I am just going to say that somebody

should not be more or less coerced into coming up with a number if you don't have a basis either. I think that should be the last option, I can't give you a number.

DR. LOCKWOOD: Dr. Perlmutter?

DR. PERLMUTTER: I am also not going to give you a number. I feel very strongly that this is going to be an issue where, if the pregnancy rate is high, the manufacturer is not going to sell his product unless he can, in fact, show that there are side effects that are so beneficial that the patients are going to love this product.

So, it is very difficult for me to give you a number on that because if you tell me that your pregnancy rate is 10 but you are going to cure ovarian cancer, I am going to look at that product very seriously. So, it is very difficult for me to give you a number.

DR. LOCKWOOD: It depends on the indication.

DR. TRUSSELL: It just depends.

DR. LOCKWOOD: Dr. Shanklin?

MS. SHANKLIN-SELBY: I am also abstaining. I don't feel qualified or comfortable enough with statistics to give a number.

DR. LOCKWOOD: Dr. Gillen?

DR. GILLEN: It is absolutely impossible for me to give you a margin for inferiority without knowing what the variability in the active control is. I cannot do it. If you told me that the active control came up with a Pearl Index of 7 and my threshold was 4, then I am willing to accept 11 at that point. I can't do that. And, you have just told me that we ran confidence intervals from 1 to 6. It is completely impossible.

So, first I would go back to historical meta-analyses and first try to clear them up and clean them up as best I can, try and quantify the variability across the active control that I am going to choose, determine what the variability in that active control is, take the lower confidence limit of what that is, the worse-case scenario, and then I would start defining my delta off of that because that is really going to put a bound on what

I am willing to accept for a new treatment efficacy and what is coming up. There is no possible way that I could just give you a flat number.

On top of that, it is going to go with what was just mentioned, what are the safety profiles of this; what are the new potential benefits. If nothing else is going to benefit me why would I accept anything lower for an efficacy?

I mean, it is very much case dependent and it is absolutely, for me, impossible to tell you what a margin is without actually knowing and quantifying what an active control point estimate and variability is.

DR. LOCKWOOD: So, you can see why we avoided answering this question yesterday--

[Laughter]

I want everybody to venture a comment because I think it is very useful, but I think the context is important. You have heard different discussions, statistical arguments, and so forth, but also arguments about exactly what the agent is going to be used for. You know, is the indication

so exciting and interesting and great, or its potential utility clinically, that we would accept a failure rate of 20 percent? It might be if it really did cure ovarian cancer. So, we are going to do the best we can with your charge but it is a tough charge. Dr. Blumenthal?

DR. BLUMENTHAL: First of all, I was hoping I would be the first person to abstain.

[Laughter]

But that thunder has been stolen! The second thing I wanted to say was we are having enough trouble in the room dealing with delta, non-inferiority, upper bound of the confidence limit--I can't wait to see that translated into a label. That rests with the agency.

So, I am just going to say again that there is room--I think Dr. Stadel mentioned that yesterday that there is still room for an open-label efficacy trial where X number of people take a drug, X number of people get pregnant. You know, it is a pretty simpl* outcome issue and you get a number which a lot of people are going to

understand. It may not be a perfect number but there is no perfect number. So, I think there is still room for that.

Getting more to the point of my abstention, I don't think that a number is particularly meaningful or productive and, in fact, in some cases it can be counter-productive. If the agency now hangs its hat on a number and an application is made for a drug which really has few side effects, has a terrific safety profile from everything that we can determine, but happens to be relatively less effective than other drugs about which we know, that is a counseling issue. We heard a comment before in the public session that we need more options. that you can't have really enough options.

Abbey made the comment yesterday that we have diaphragms on the market. We recognize, certainly, that they are less effective than hormonal contraceptives and, yet, they are approved. So, as I think I mentioned before when Johanna made her comment, the number just depends.

It depends on the characteristics of the agent and it depends on what the characteristics are relative to other agents. Does that mean there has to be a comparator in order to get it approved? I don't think so.

That could be useful and it could be useful especially if you don't have enough of one type of person in a trial. So, let's say, as we have discussed, we want certain subgroups represented in an application if an application is made even on the basis of an open-label trial and certain subgroups are not adequately represented. You could have an approval, but with a recommendation that Phase 4 studies be conducted to flesh out some of those missing subgroups and sort of complete the database.

I do think that it might be more meaningful to start talking about classes of contraceptives. I think that was also brought up a few minutes ago. That takes the onus off a number and puts us in ranges. Yes, there could be a slippery slope and you could conceivably have some

hormonal contraceptives that are in the same class with barriers because, hopefully, barriers are going to get better. So, I think the concept of classes of hormonal contraceptives based on range of effectiveness might be much more useful.

DR. LOCKWOOD: We will try to keep these responses to about a minute. Dr. Gibbs?

DR. GIBBS: This has really been fun!

[Laughter]

I can't remember the last time I was on a committee when so many people squirmed and the leader of the committee was pressing everyone so hard! I am also going to take more than a minute because I have been quiet all morning.

We know how these estimates can be manipulated. If we arbitrarily set a limit, then we are going to get what we don't want. We are going to get highly selected data. In general, I am opposed to paternalism or, in this case, maternalism. I am also generally opposed to arbitrariness. What I am in favor of is disclosure and labeling.

Now for the number, being opposed to paternalism and arbitrariness I do it in my job every day, just as you do. We have one convention that has stood the test of time and we use 95 percent to say that something is meaningful or significant. So, I would say I would accept any value in effectiveness as long as the upper bound of that is 95 percent for a contraceptive to be considered highly effective. That picks up on Paul's idea that, yes, we have contraceptives that are approved but really some are highly effective and some are less effective.

DR. LOCKWOOD: And that is in an active control.

DR. GIBBS: Yes.

DR. LOCKWOOD: Dr. Trussell?

DR. TRUSSELL: I will make two points. One is about the delta. The delta has nothing to do with statistics, other than plugging it into a formula. What the delta means is what you, as a clinician, think is--you are clinically indifferent about. You are indifferent that something in the

range of delta is not clinically meaningful or important to you.

Then it becomes clear that you can judge delta only in relationship to what you think, for example the historical truth is, or what you think the active comparator should be. Let's say that is 30 mcg pills, 30-35 mcg pills. In my heart of hearts I do not believe that any reasonable clinical trial will produce a result, if you pool them all together, that is above 2 even if you include all the kinds of candidates in the trial that we have excluded before.

But, in my heart of hearts, not being a clinician, I do not believe that I am clinically indifferent between 2 percent and 6 percent as a failure rate. I don't think that those are the same. I wouldn't recommend that anybody use the product that has a 6 percent failure rate when there is a 2 percent failure rate product, assuming that the other benefits or risks of the product were the same. So, I personally wouldn't go above a delta of 2 even though I am not a clinician.

The second point is that I would be willing to trade off, as many have said, efficacy for something else. One particular thing I would be willing to trade it off against, which the FDA does not consider but I would consider to be highly important, is cost. If there were a pill known to have a 10 percent failure rate that cost a dollar a cycle, put it on the market.

DR. LOCKWOOD: Dr. Westney?

DR. WESTNEY: I will also not feel guilty in abstaining, primarily because I do not prescribe this class of drugs and I had never heard of a Pearl Index before preparing for this meeting and I am now finding out that this descriptor is on the verge of becoming obsolete and generated in groups that do not reflect the populations, rather, the patients that we are trying to utilize the drug and get data on.

DR. LOCKWOOD: You are forgiven! Dr. Espey?

DR. ESPEY: Well, despite the fact that the statistics are a little over my head I am going to

agree with Dr. Gibbs, which I think actually is similar to what Dr. Trussell just said. You know, 95 percent would be my cutoff.

A couple of things just qualitatively, and I think this may be sort of a moot point because really what we know about most oral contraceptives is that they are highly effective. So, it is hard to imagine a drug getting to the point of going through Phase 3 trials that has a 10 percent failure rate, however you look at it. So, I think just taking a step backward, most of the drugs that are going to come to be looked at in this kind of critical fashion, my guess is they are going to be in that highly effective category.

The other thing is I think it was really helpful this morning to get the public commentary from the women's advocacy groups, that it is not just the clinicians or us that feel that it is reasonable to have a tradeoff between efficacy and side effects but these advocacy groups feel the same way. So, I think that does allow us to look a little bit downward in terms of what we feel would

be an appropriate limit for efficacy.

DR. LOCKWOOD: Dr. Peterson?

DR. PETERSON: I think there are two issues that we have touched on that make it difficult for people to come up with a number. One is the human issue. Bruce talked about the consumer perspective. He abstained, trying to guess what the consumer perspective would be. James talked about the provider perspective. The problem is that we can each speak to our own perspective as providers but we really don't know what providers nationally might think because those data aren't available. Likewise, we don't know what consumers nationally might see.

So, we can take James' point, and he said a number of things that I would have said. If it is 2 percent and we pick a delta of 4 and, let's say from my perspective, there would be a meaningful difference between 2 and 6. Then, that is my perspective.

I think while our perspectives will differ potentially, the guiding principle is that people

deserve to be informed about that difference, whatever the acceptability of that difference seems to be one that is not being contested.

So, I think that gets us then to the statistical realm. First was the human realm and providers and consumers and what is meaningful. Then, the second is how to determine whether or not we have obtained the truth about those measures. That is the issue of precision.

So, I think there are these two elements that we have to decide. I don't know that we can come up with something that is a specific number that would really represent what people believe to be meaningful, but it is probably in that range where 2 percent is okay because that is what we believed with use as indicated. One or 2 percent is a failure rate that people have been talking about. That raises this issue of Slaughter's slippery slope and the comparator because that is really what we have been talking about with respect to the 50 mcg and the 30-35 mcg. We think it might be true for the 20s but that is less well

documented, particularly among subgroups.

So, the issue of 1-2 percent, saying if it is a meaningful difference, probably it is going to be somewhere around 5 percent and 10 percent that you are going to get consensus aboutB-yes, that is different. So, I am not sure that we can help much between the 5 and 10 percent range but that is probably where you get 90 percent of the group of people say, yes, that is different.

Then I think the issue is the statistical issue and saying, you know, how confident are we that we have assessed that meaningful difference that most people would probably agree is there.

DR. LOCKWOOD: Dr. Berenson?

DR. BERENSON: I think I know why we avoided this yesterday. It is a pretty complicated issue. The first one, as people said, is what will the pill be taken for. If you are dealing with one of the other indications that we prescribe pills for, dysmenorrhea or acne, then efficacy may not even be an issue if you are certain that that patient did not need it for birth control because

they were not sexually active, or perhaps even had their tubes tied. We have people after sterilization that want some birth control pills for other reasons.

A second issue; so, you would want to be able to give those people a very low-dose pill and advise them that it is not as efficacious for birth control.

Then, you also have special populations that we haven't addressed very much. For example, you may have a patient with migraine headaches that can't take higher-dose pills but she doesn't have aura, so she wants a lower-dose pill.

The other issue that is complicated is that we are talking about perfect use here, I am assuming, and if typical use goes up because side effects go down, then this is going to be stronger than any data on perfect use for most of your patients.

So, I don't really know how to answer this question, except to say if I have a patient that I am certain is going to take those pills every day

and she can use any birth control pill on the market, I want to give her the one that works the best, that doesn't have more side effects than any other. So, most important is just to have the data. If you want to know what doesn't matter, I would agree with about 5 percent and there I am probably going to tell her they are pretty equally effective. Over that there are definitely going to be some warnings.

DR. LOCKWOOD: Dr. Tulman?

DR. TULMAN: I thought we weren't going to answer this yesterday so we have to answer it today. We have gone through several iterations. We originally started with the Pearl and then, after discussion, sort of said, well, we are not going to really keep the Pearl because it maybe has its own statistical problems.

Then we talked about the theoretical effectiveness versus actual effectiveness and we decided that we really need to think more in terms of actual effectiveness rather than theoretical or best-use effectiveness. Now we seem to be going

back to best-use effectiveness, which doesn't exist in the real world.

Then we talked about safety of the pill in terms of life-threatening effects and how do we check for that, and it has to be postmarketing because we need huge samples to perhaps really try to nail it down in terms of the life-threatening side effects.

So, if we have a new drug coming to market, it would seem that, unless the new drug, in terms of theoretical effectiveness using the Pearl, which we are not going to use, is at least around a 2, it would seem that it wouldn't capture any market share unless it has some other handle such that it is better for acne or it is better for some other side effect, makes you look like Cindy Crawford or something, something that they could really market as a handle.

So, it seems that we are dealing with numbers that are hard to put a precise estimate on because if the new product is not as good as what is there it would seem that clinicians aren't going

to prescribe it unless there is something else about it, and that something else has to be perhaps shown in Phase 3 but it may not be able to be shown until Phase 4 anyhow in terms of being truly safer for the serious side effects. Therefore, I am going to decline to put any numbers around anything. That was a long-winded answer to say that.

DR. LOCKWOOD: Dr. Scott?

DR. SCOTT: Charlie, I am going to answer but I am going to try to do it in a way that just a simple document and patients can understand. I think to really answer this it requires a survey of women. We already heard this morning that there are many reasons that women might want a pill that is less effective. There are plenty of other methods that are less effective than whatever this pill will be.

So, I wouldn't even put a limit on it, I don't think, as long as it is disclosed and the information is easily available to docs and to patients in a way that they can understand, simple

and understandB-if you take this new pill your chance of a pregnancy in 1 year in 100 women is 4 percent. If you take the other one, your chance of pregnancy in 1 year is 2 percent. I don't like the Pearl Index either, but I am just saying I don't think there is any reason for a limit if there are benefits from the new pill. That is the way I look at it.

DR. LOCKWOOD: Dr. Bustillo?

DR. BUSTILLO: I keep asking myself why do we need more oral contraceptive combinations. I am an infertility doctor--

[Laughter]

I use the birth control pill for completely different indications. My patients are suppressing their cycles before we do IVF, etc., and my favorite pill is the 1/35. So, there you go. So, I would have a really hard time as a woman, if I were in the reproductive age range, tolerating something that would have a 5-time failure rate unless, as has been mentioned, you had a significant reasonB-you know, if I don't tolerate

the 20s because my breast pain is so bad I am willing to take a 5-time pregnancy rate and take the 10 because now my breasts don't hurt.

So, that is the way I would look at it. But I am worried about the slippery slope because what are we trying to do, we are trying to prevent pregnancy. So. I mean, we have to perhaps tolerate some things to accomplish something else. So, every day I say why do we need another pill? Why do we need this? Why do we need that? And, I am using generic 1/35s for endometriosis prevention, period, because maybe it works better because it might suppress gonadotropins better and that is what I want to do with my patients.

Anyway, I don't know what the number is but I think that for me more than 5 times the pregnancy rate would be outrageous unless you had significant reason to want to prescribe that.

DR. LOCKWOOD: I will vote and then we will do that. This is a mock vote, I guess we could call it. I am going to give the answer that everybody I think gave, which is it depends. I

think Dr. Trussell is right. If this is an ordinary contraceptive that doesn't make you look like Cindy Crawford, that doesn't cure ovarian cancer, that doesn't have a number of other potentially useful, beneficial side effects, positive externalities, I think 2 is a very reasonable number.

But if you tell me that it is going to do all these other things, that it is likely to do it, there is biological plausibility for that argument or there is a frank indication for those other potential positive effects, then I am not sure what the limit is. Caveat emptor would be in the labeling and people make their own decisions.

DR. MONROE: May I ask you for just one clarification and then I am going to let you off the hook here? When you give this number 2, the number we work with is from a clinical-trial environment, are you talking about the actual use or the perfect use in the clinical trial? I ask both you and Dr. Trussell to just clarify that for us.

DR. LOCKWOOD: Yes, I will answer. I am talking about in the context of that clinical trial. It is not perfect use because we have potentially broadened the entry criteria, but it is certainly not typical use in the real world. It is going to be probably much closer to--I don't think it will be substantially different than the current results from trials that are being done, but it will, hopefully, be more reflective of the population. So, it is not quite perfect use and it is not quite typical use.

DR. TRUSSELL: It is typical use in the clinical trial, all pregnancies, all exposure.

DR. LOCKWOOD: Dr. Gillen.

DR. GILLEN: I would just like to suggest an algorithm potentially for the FDA to go about thinking about this problem, to kind of take it step by step. If you are going to design an active control trial, the first thing that you must do is define what the active control is. It is nearly impossible to find what a delta is without knowing what the comparative is.

So, we first need to think about what will be the active control and we have talked about issues with that. Will it be time and variant? Will it be something that changes as time progresses? Will you get into problems if it is changing as time progresses because people are worried about the ramping up of thresholds as things go along. So, that needs to be considered there. It should also be based upon what is most popular in terms of use; what is the standard of care right now when you are defining the active control.

The next thing that I would do is then I would think about what the point estimate for that active control is, and what is my confidence in that point estimate through the trials that have been done in the past and the postmarketing surveillance that is being done, etc.

From there, I would come back and I would say, okay, now what would I be willing to accept for a one-year failure rate on a new therapy? If my clinical threshold for that were 95 percent, for

example, I would not go less than 95 percent. Then I would go back now to my active control and say, well, what could the point estimates for my active control be and that then defines my delta.

My worst-case scenario is what is the 95 percent confidence interval for the past point estimates on that active control? If it turned out that they were 94 I am only willing to accept a 1 percent difference at that point for the difference in those two. I don't want to be any worse because it certainly could come out to be that you only have a difference of 1 percent and, you know, you are falling below your threshold.

So, I think that Dr. Trussell made a very good point in saying that this is a clinical measure that you are defining, but first you have to set the stage and say what the frame of reference is here. And, the frame of reference becomes what that active control is and then what you are clinically willing to accept relative to what active control is.

DR. LOCKWOOD: Does either Diana or Dr.

Trussell want to respond to that?

DR. PETITTI: I only want to withdraw maybe my 4. But I think I was working from what I call a prior, which is an implicit prior based on what I heard from the people from the FDA, and maybe it is not true, which is that in contraceptive trials there is this benchmark of 2 which has no variability, and that, in the past, or that there is a 95 percent confidence interval within trials of the size that the FDA has required in the past that would accept up to--the upper bound of those confidence intervals are 6.

So, I just wanted to explain why I was able to come to a number based on the fact that I think we have prior information that allows us to choose a 95 percent confidence. But it is very clear from what we have heard that if the pill is no better, has no benefits over anything else, one could make an argument for accepting no difference, a delta of zero. The point is why do we need yet another contraceptive if, in fact, it doesn't have offsetting benefits?

DR. LOCKWOOD: Dr. Berenson?

DR. BERENSON: I may be missing something here, but I thought that yesterday we looked at data that over half of women missed at least one pill in a cycle and about 20 percent missed at least three in a row. So, from there we have gone to stating that the pills have to be 98 percent effective which means that they still have to work most of the time if you are missing three pills in a row, which is not how I counsel my patients. So, I thought that the 98 percent we were talking about was perfect use or near perfect use.

DR. LOCKWOOD: Maybe, again, we are confusing typical use, real world which may be up to 8 percent failure rates, which are fine, versus a clinical trial where you have many, many levels of control and encouragements of compliance, and so forth, even in the context of now broadening the entry criteria. Dr. Trussell, do you want to comment on that?

DR. TRUSSELL: No, I was talking solely about clinical trials and I gave my answer for what

I thought the comparator should be, which is 30-35 mcg pills, and I gave my guess about what I thought the failure rate would be in one year in an expanded population of users, which is 2 or less, and my delta would be no more than 2.

DR. LOCKWOOD: I think we are talking about two different things, but I think we have now given the FDA quite a bit of personal opinion, thoughts, ranges, numbers.

DR. MONROE: Yes, you have made it clear that it is not real clear.

DR. LOCKWOOD: It depends! In accounting, as accountants love to say, it depends!

I just want to summarize briefly what I think our consensus responses are to the questions raised by Phase 4 commitments. I think we have provided, by endorsing Dr. Petitti's presentation, the different design possibilities that can be employed whether looking at safety or potentially efficacy in Phase 4 trials, with the thought that there may be some settings where a randomized clinical trial might be in order.

In terms of Phase 4 commitments generally confined to obtaining information related to safety, I think we have said that, in fact, we can also look at real-world actual-use product effectiveness, and provided some insights into how that information could be obtained.

The last question which we didn't address is, in addition to thrombotic and thromboembolic risk, are there other safety issues that should be addressed within long-term or large Phase 4 studies? I want to spend the last five minutes talking about that specifically.

DR. BUSTILLO: I think of concern to women always is breast cancer. I had a phone call from a reporter before I came here to ask me about continuous-use birth control pills and is that going to cause a greater incidence of breast cancer. So, I think that.

I think also the benefits ought to be looked at, you know, incidence of endometriosis perhaps, dysmenorrhea, whatever. I know the more you add the more costly, but I think some things

like ovarian cancer, endometrial cancer, breast cancer ought to be looked at.

DR. LOCKWOOD: I mean, you would have to design such a trial that you paid them enough to continue for a year and then observe the amount of bleeding they did. I think that, in general, though, when you look at their endometria, they become progressively more atrophic and there is literally less surface area to bleed.

Talking about breast cancer, this has obviously been a highly contentious and somewhat controversial topic but, through prodigious statistical efforts assessing long-term outcomes in over 100,000 patients, the consensus is that there is a very minimal but potentially positive effect. It probably is beyond the scale of a safety trial to address that outcome which is, in fact, probably substantially rarer than venous thrombotic events. But I don't know if anybody else has--

DR. BUSTILLO: But I think the comment is that, if you are administering it differently--you know, it depends on what you believe. If you are

going to go to a 364-day pill, or whatever, then is that the same as what we use now?

DR. LOCKWOOD: I think the same arguments can be made about stroke and MI as well.

DR. BUSTILLO: Sure, absolutely.

DR. LOCKWOOD: Dr. Gibbs?

DR. GIBBS: I just wanted to add to Maria's list of benefits protection from pelvic inflammatory disease, and then consider the whole issue of sexually transmitted diseases in general.

DR. LOCKWOOD: Dr. Stadel?

DR. STADEL: In this context, there had been a question earlier about non-contraceptive benefits, there is a whole range of non-contraceptive benefits and harms in the literature. Many of them go back to pills that are higher dose than currently. And, if this sort of information really does need to be considered in the light of what is currently used--I think for example the protection against benign breast disease was pretty convincing, when I reviewed the literature, that that was the function of higher

progestin doses that are currently used. So, there is a whole area here. I just want to provide a general caution that applies to all of the issues of non-contraceptive effects as well as, of course, efficacy.

Many of them do appear to be dose related and it took the literature ten years at least to catch up because the studies require a large-scale population exposure before the study can be done. So, I just want to make that clear.

Thank you.

DR. LOCKWOOD: Is there consensus beyond thromboembolic disease for safety outcomes? I don't sense that there is a consensus. These are certainly worth studying and, hopefully, people will but is there consensus that that really ought to be high priority for the FDA to encourage? No? No consensus? Yes, consensus? I don't think so. Then, let us break for lunch.

DR. WATKINS: We will reconvene at 1:30 and, committee members, your lunch arrangements are the same as yesterday.

[Whereupon, at 12:25 p.m., the proceedings were recessed for lunch, to reconvene at 1:35 p.m.]

AFTERNOON PROCEEDINGS

DR. LOCKWOOD: I am going to take the chair's prerogative and summarize our conversations regarding a number of discussions that were had. I think it is fair to state that the consensus of this committee was to encourage the FDA, as they approach the assessment of sponsor applications, to have great flexibility in terms of accepting an efficacy rate, such that we don't create artificial restraints to entry of new potentially efficacious and safer products and, at the same time, that there isn't creep of failure rates.

There was no consensus on a number. There was no consensus on the upper confidence interval. There was certainly no consensus on a point estimate. I think what there was consensus on was the concept that it depends. It depends on what the agent is being proposed, what the indications are, and what the potential biologically plausible benefits might be to that agent.

So, you heard upper confidence intervals of 6 and you heard upper confidence intervals of 3,

in my case. But it depended on the context and not on any absolute arbitrary number. I think that each drug has to be weighed in terms of its risk and benefits and there will be tradeoffs that will, by necessity, have to be made in terms of safety and efficacy.

So, this committee I think is very clearly stating that we don't want to be tied down to a specific interval. We are quite tolerant of fairly large intervals if there are potential benefits and additional positive externalities and side effects that might accrue a given agent. And, we don't want an arbitrary number to be ascribed. We don't want an arbitrary number to be ascribed--we certainly don't want it to appear to industry or to the lay public that from now on no agent will be approved unless it has a point index of less than 2 and an interval of 3, or something like that. Just the oppositeB-flexibility. We want to encourage the development of new agents that will provide a greater menu of opportunities for treating patients in an individualistic manner.

With that comment, we are going to move on to the next section, and then we will come back later. So, Dr. Soule will discuss labeling.

Topic 7 - Labeling

DR. SOULE: Good afternoon, everybody.

[Slide]

I am Lisa Soule. In preparation for our discussion of labeling I would like to describe briefly the FDA's new labeling initiative, known as "The Physician Labeling Rule."

[Slide]

The general content of labeling is specified in the Code of Federal Regulations. As you see here, labeling must contain a summary of essential scientific information for the safe and effective use of the drug. It must be informative and accurate, and neither promotional in tone nor false or misleading. It must be based, to the extent possible, on data derived from human experience. No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or lack of substantial evidence

of effectiveness. Finally, labeling should be updated when new information becomes available that could cause the labeling to become inaccurate, false or misleading.

[Slide]

Research was done recently through the use of physician surveys, focus groups and public comments to evaluate the utility of labeling to prescribers. The findings show that healthcare providers use labeling primarily to find a specific item of information or to answer a specific question. In other words, very few of you are sitting down and reading the 40-page label end to end.

Also, healthcare providers found the existing format difficult to use, especially when trying to find a particular piece of information. They wanted easy access to certain labeling sections that they find more useful or more important. And, they would use labeling more often if it included a short, as in a maximum half-page length, synopsis of the information found in the

full label. The Physician Labeling Rule was enacted to address these needs, in January, 2006, and will apply to all applications submitted subsequent to June 30th, 2006.

[Slide]

Among the novel aspects of the new labeling are a section for patient counseling information, which is to help healthcare providers advise patients about important uses, limitations and risks of the medication. In addition, the new label encourages reporting of adverse events by providing contact information right on the label. It identifies and dates recent major changes in some of the major areas of the label, including the boxed warning, indications, contraindications, warnings and precautions. And, it adds the date of the initial U.S. approval.

[Slide]

The basic structure of the new labeling now includes an initial half-page summary of the most important and most frequently referenced information in the label. This is known as the

highlights section. The label also includes for the first time a table of contents. As labeling is increasingly available in electronic form, for example on the National Library of Medicine website, the new labeling format will allow hyper-linking of text. So, for example, from the summary information that you might read in the highlights section, you can jump right over to the full prescribing information to get additional information. The labeling also reorganizes information such that frequently referenced information is moved forward in the label while safety information remains consolidated.

The highlights section contains brief summaries about the following sections; the boxed warning, indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

The additional information found specifically in the highlights section includes the

U.S. approval date, the recent major changes made to the label, the adverse reaction reporting contact information, patient counseling information and any labeling revision dates.

[Slide]

Following the highlights, there is now a table of contents. Again, in electronic format this will then hyper-link into the specific sections. As you see, now the label actually starts with the indications for the drug, which formerly you had to get to the latter half of the label to find.

[Slide]

Other format changes include consolidation of the warnings and precautions sections. New sections that were formerly subheadings under precautions are now stand-alone sections. Specifically, these are drug interactions, use in specific populations and patient counseling information. Formerly optional sections are now required, specifically a clinical studies section and a section on nonclinical toxicology.

[Slide]

In addition to the Physician's Labeling Rule, guidances for industry have been issued concerning the clinical studies and adverse reactions section of the label, and a draft guidance has been issued concerning the warnings and precautions, contraindications and boxed warning sections.

For contraindications, items should be listed there if the risk from use clearly outweighs any possible therapeutic benefit. In contraindications this is intended to include known hazards only, not theoretical risks. Currently, hormonal contraceptive labels list about 15 contraindications to use.

To be in a boxed warning, an adverse reaction should be so serious that it must be considered in assessing the risks and benefits of using a drug, or it could be an adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug. Currently, the only boxed warning that we have on

hormonal contraceptives concerns smoking and the increased risk of cardiovascular events.

Then, there is another, slightly lower hierarchy of warnings we call bolded warnings. These are warnings emphasized with bold type but not placed at the front of the label as a boxed warning is. For example, warnings of the risk of hyperkalemia with certain progestins, or a warning that the product doesn't protect against sexually transmitted infections.

[Slide]

Under the new guidance on the adverse reactions section, an adverse reaction is an event reasonably associated with use of the drug, meaning that there is some basis to believe in a causal relationship. This section should identify the most important adverse reactions, and this might be on the basis of frequency, such as adverse reactions that occur in at least 10 percent of the population or that occur at twice the rate you might see in a placebo group, or it might be adverse reactions leading to intervention, such as

discontinuation or dose changes for the drug.

The goal of this section is to avoid laundry lists, which we sometimes see now, where you have lots of low frequency adverse reactions that may have no plausible relationship with the drug. Currently, our hormonal contraceptive labels list both class adverse reactions as well as those noted in trials for the specific drug being labeled.

[Slide]

The adverse reactions section is also intended to be updated as new information is obtained. Some of these sources of information could be controlled trials or epidemiologic studies done after marketing approval, as well as analyses of postmarketing adverse event reports.

[Slide]

A newly required section is the clinical studies section. Although we have typically included these in our labels, this requirement is new to the Physician Labeling Rule. Among the features that should be described in this section

are aspects of the design that may have implications as to how well a study's findings will generalize to the target population of users such as duration of exposure, population demographics and methods used in the trial that may have facilitated compliance.

[Slide]

The Physician Labeling Rule initiative offers new opportunities to provide more informative labeling such as new patient counseling information section, newly required clinical studies section that may help in translation into the real world, and new rules for the safety sections that may help focus on the most relevant safety issues and allow for timely updating.

In summary, we believe this will offer us new opportunities to create labeling that will better serve patients and prescribers. Given the new format in which we will need to develop labeling, we look forward to discussing with you how patient and prescriber needs can best be addressed.

DR. LOCKWOOD: Thank you. Any comments on the presentation?

DR. SCOTT: Do you have many guidelines for that synopsis, which is what everybody is going to read?

DR. SOULE: The highlights section?

DR. SCOTT: I think you said at the beginningB-is it going to be a standardized sort of synopsis or abstract?

DR. SOULE: Yes.

DR. SCOTT: So, you have to include certain things in it?

DR. SOULE: Right. Let's see if I can get back to the slides.

DR. SCOTT: Maybe I missed it.

DR. SOULE: I will get that slide up again and show you. There are some detailed specifications, one of which being that it cannot exceed half a page in length so we really are trying to keep it focused and short enough.

DR. SCOTT: But what I am getting at is do you have to--

DR. SOULE: Is this the kind of information you are looking for as far as what would actually be contained in it?

DR. SCOTT: Yes, does it have the efficacy and major side effects? I guess it does.

DR. SOULE: Yes, this section of the label would not contain, like, a full clinical studies description for example. There certainly will be flexibility in how we populate these areas but these are the major areas that would be included.

DR. SCOTT: I am just wondering whether it would be like sort of a structured abstract where they have to include this, this and this.

DR. SOULE: Some of the items are structured. Certainly anything with a boxed warning, or at least a very concise summary of the boxed warning needs to be included there. Indications and usage is, again, summarized but it is going to be more or less verbatim what the indication is for the drug. If there is no information on use in specific populations, for example, that might not be something that you would

find in a given label.

DR. TRUSSELL: Where does the information on effectiveness go?

DR. SOULE: Typically, we have had that more confined to the clinical studies section in terms of actually quoting pregnancy rates, and things like that.

DR. SCOTT: When you list all of these things, how long will that one be?

DR. SOULE: The full label?

DR. SCOTT: This new format? When you start listing all the studies, and so on, and references, and so on, how long will that be?

DR. SOULE: Well, given that we already do have to discussion of clinical studies in our labeling--you know, for some drugs that may be a really new requirement. For us, in our division, that really is not something that we haven't already been doing. So, I don't think that will necessarily expand the length of it. If we look at some of the other options, I think some of the consolidation of safety information will reduce

some of the length of the label.

DR. SCOTT: This is all hard copy, I guess. Is that what you are saying? That will go out to the doc?

DR. SOULE: Right, we are talking about the package insert first of all but, again, much of this is also available in electronic format too.

DR. SCOTT: That is why I was wondering have you considered certain things that may be investigators or somebody might be interested in, like the reference and so on, just to put them in electronic format.

DR. SOULE: Well, the intention is that all labeling will eventually be available on the National Library of Medicine website.

DR. SCOTT: But clinicians don't use that. You know, they use what comes across their desk, and so on, but investigators do. But I am just trying to say, you know, is there a concise way to get this across to docs and patients? I don't know how long this will be.

DR. SOULE: Well, I mean, we are now within

the eligibility period so basically the next oral contraceptive or hormonal contraceptive application submitted will fall under this new labeling rubric. So, I think it is something that you will be seeing in the relatively near future.

DR. LOCKWOOD: Dr. Gibbs, Johnson and Peterson.

DR. GIBBS: Well, this is a most welcome change. Congratulations for bringing it to this point. I have a couple of thoughts about the patient counseling information. I could see that this could be either aimed at the provider by saying these are the points you should cover, or it should be aimed at the patient by saying these are the points that are very important to you. I think we would facilitate the counseling if, in a standardized fashion, these points would be aimed at the patient.

DR. SOULE: Yes, one of the things I didn't mention here, but the intention also is that at the end of this label, if there is an approved patient packaging insert, which most of our labels do have,

that would also be appended to the label so that would also be available.

DR. GIBBS: But the patient information forms, at least that I read for the medications I take, they are pretty convoluted also and really making it a user-friendly document for someone with whatever level of education you target would be a great service.

DR. SOULE: Yes, that certainly is an effort that we do continue to make.

DR. JOHNSON: Just to better understand, the addition of bolded warningsB-you are right; the only boxed warnings on hormonal contraceptives are smoking and cardiovascular risk. But the bolded warnings came up earlier today in discussion and I am wondering, first, where those will go and, secondly, how those are determined to go into the labeling. How is that decision made? Because I think that was unclear to providers in how that decision was made regarding the product we discussed or that came up earlier.

DR. SOULE: We have a lot of interaction

with our Drug Safety Office and very often, particularly with postmarketing reports that might indicate need for some additional labeling, decisions to be made with those folks. It is basically a review decision after reviewing whatever new data we may have as to the level of a warning that is needed.

DR. JOHNSON: So, new data is required. So, in this circumstance new data was acquired and, therefore, greater risk was assumed although greater risk has not been shown? I am just wondering how you got to the bolding of this warning without data showing an increased risk.

DR. SOULE: I should clarify that. There can be a couple of different scenarios. Companies can propose, of their own initiative, to add safety information to the label. In that case, they typically just inform us of the change they are planning to make. It is not something that necessarily needs prior approval from the agency. I don't know if Dr. Monroe wants to address the specifics of this situation.

DR. MONROE: Well, I will just mention we do have some generics, as you have mentioned, in terms of smoking and its relationship to cardiovascular risk. Then, in certain products there are perhaps bolded warnings. But we are not really supposed to be talking about specific products today and what may or may not have led to a labeling of a specific product.

If we are just talking about concept and what would do it then it is as Dr. Soule has said; it has to become a judgment call based on the perceived health. In other words, we do a warning. A warning can be put in there also as sort of preemptively in the sense that if we believe that certain prescribing-Band, Lisa, you can correct me hereB-it should affect your prescribing or not and you can perhaps avoid a certain problem, like with smoking. That could be one of the bases. Another basis would certainly be what has been observed either in a clinical trial or what may have been reported from post-approval adverse events.

So, there are a number of conditions that

trigger it but, again, as to whether it gets bolded or not has to be ultimately a judgment call that is made by a group of individuals who make their best assessment of it.

DR. JOHNSON: The bolded clearly is important because that gets a lot of physician concern. I guess I just want clarification on how that was decided, not in this specific case but how it could be decided in any case. Is it always based on scientific evidence?

DR. MONROE: I am going to be bailed out here. Go right ahead, Dr. Shames.

DR. SHAMES: I am Dan Shames. I was the previous director and now I am in the office that oversees reproductive and some of the other divisions. What I have heard here about this issue is that, of course, physicians are concerned that we might be over-reacting or putting out material there before we absolutely have very strong evidence that there is a real safety risk. There may be, say, pharmacokinetic data or other data, or other signals.

You have to understand the entire context of what is going on here. We are in an environment where there is great concern among the public, and public officials, and all sorts of groups that we have not been as transparent as we should have been perhaps with information that we have and it takes too long for us to publish our deliberations, etc., etc.

So, when we get information that we think some people might think is important related to safety we may feel that that is important for us to get out there even though we may not have the exact precise clinical implications of that.

Now, I know that it is a problem for some groups. For other groups it is what we should be doing. I mean, there are people who think that when we publish certain information, as you have referred to, perhaps the drug should be removed from the market. There are other people, like you, that perhaps say, well, we should be doing large epi. studies, or whatever, to find out the precise information before we publish that. So, we are

constantly in tension about these things.

I think what is happening, which it appears the general public wants, is more transparency, in a sense putting some of the burden, in terms of risk management, more perhaps on the physicians and the patients than, you know, just being more paternalistic and having it all within the FDA and we finally decide, well, this drug is no good, or something like that, which may be too late in the view of some people and if we had published the information sooner and they had known about it, that would be better. So, these are some of the large kind of public-policy issues that go into some of these decisions.

DR. JOHNSON: I guess my main question is, is there a standard for using this type of warning and is there a standard that the FDA uses? I would really be concerned if it was politically based in any way.

DR. SHAMES: The general standard is do we think that for some people this might alter the way they prescribe or use the drug. For some people

some of this information does affect the way they prescribe or use the drug.

Now, there are various guidances that are associated with this new labeling rule. There are three of them. They are on the FDA website. They precisely lay out when there should be a warning. It is much more spelled out now than it used to be. So, you can actually go and get these guidances on the FDA website and it will spell out preciselyB-as precisely as we can, under what circumstances there will be warnings and precautions, etc., etc.

DR. JOHNSON: Could you tell us briefly what those guidelines are?

DR. ESPEY: I have it right here.

DR. SHAMES: I don't know the guidance verbatim right now but I think generally it has to do with changing prescribing patterns. I think, in the case of a contraindication, we may have to have some more robust scientific basis for it, something like that.

DR. SOULE: Yes, as I mentioned, contraindications are intended to be based on

known, documented hazards, not theoretical risks. As far as the detail, it is a lengthy document. As far as the rest, I also can't cite you specific points but the document is available on the website, as Dr. Shames indicated.

DR. JOHNSON: And that is fairly new?

DR. SOULE: That was issued within about the last nine months or a year.

DR. JOHNSON: So, from now on any warnings are going to meet one of those three criteria?

DR. SOULE: There are probably more than three criteria listed in the guidance, but yes.

DR. JOHNSON: So, they are going to meet one of those criteria and the decision will finally be made by FDA whether or not it meets those criteria, needs to be added to the labeling.

DR. SHAMES: Clearly, there are going to be situations that might be of concern to certain people that we are never going to know the precise answer. So, we probably might tend to give out this information more aggressively than perhaps we did before because I think that is what people are

asking us to do. But there are a lot of questions that we have had here that will never be answered. Some of the things we have been talking about here, they just never will have an answer. So, we have to give the best information that we have.

I mean, we don't give out every bit of trivial information. For example, I think we are eliminating the laundry list, which we used to have this whole list of every possible complication that you have. So, this new labeling is an attempt to standardize what we have done before, which probably was less standard than it should have been.

DR. ESPEY: I actually have the language, just a sentence from the black box warning that appears on the FDA website. It says black box warnings are meant to provide physicians with important insights as to how to prescribe a drug that may be associated with serious side effects in a way that maximizes benefits and minimizes its risks.

I just share the same concerns. I know we

are not supposed to talk about specifics but the black box warnings that are on the hormonal contraceptives I am not sure meet even this very qualitative criteria, and I know I am not alone in wondering what exactly motivated those black box warnings.

I think it is one thing to be transparent for the public, but it is another, in a country where we have a 50 percent unintended pregnancy rate, to consider the huge public health impact that a black box warning will have. Just the simple fact of bolding it can have such an effect on prescribing that my concern is that we are not actually highlighting a potentially serious side effect that really has no basis in scientific evidence.

DR. LOCKWOOD: Again, there are ethical levels of deciding between our obligations and your obligations to do what is right and providing autonomy to the provider and the patient to make their own decisions. Obviously, there are unspoken political effects. We live in a political world.

There are also legal implications. Black box labeling and warnings are used all the time by trial lawyers to try to impugn care provided by physicians. No field has suffered more egregiously by frivolous lawsuits than have OB/GYN.

So, you know, these do have implications and I know you are aware of all of them. We are particularly sensitive to them because we are in the firing range of these folks. So, I think what you are hearing from the committee is that the greatest caution should be applied in deciding when such warnings merit being placed. Dr. Peterson?

DR. PETERSON: I just wanted to follow-up on James' question about effectiveness and Ron's point about using this for counseling and Charlie's point earlier about caveat emptor. To what extent will the new labeling be used to try to communicate effectiveness relative to the discussion that we were having before lunch? What you said, it sounded like, was that that information would be communicated through the description of the clinical studies.

DR. SOULE: Well, that is typically where we have delineated the results of particular studies, but I agree that the patient counseling section is also a natural way that we would provide perhaps more patient-friendly information about this. I think, when we turn to the questions for discussion about labeling, those are some of the specific issues we would like to hear from you about.

DR. LOCKWOOD: Dr. Blumenthal, you raised your hand; you gave some signal?

DR. BLUMENTHAL: No, I didn't want to bid on that painting!

DR. LOCKWOOD: Any other questions?

MS. SHANKLIN-SELBY: You did say you were redoing the product insert that the patient would be receiving?

DR. SOULE: No, that is not covered under the Physician Labeling Rule. This applies to the package insert essentially for healthcare providers, but the rule does mandate that if a patient packaging insert exists-Bnot all drugs have

them, most of our drugs do--

MS. SHANKLIN-SELBY: I mean, you are talking about patient counseling--and that information doesn't always come through. I mean, I find it has been kind of hit or miss as far as different physicians how much information I am given. Then you read the product insert and, I mean, I understand it if I can see it. I mean, I have to use my glasses and a magnifying glass to read it.

But I am thinking of somebody who isn't familiar with a lot of the terminology. They are going to be looking at that and they are going to draw a blank. And, a lot of times doctors do not always tell you want you need to know. I mean, it is kind of up to the patient to ask a lot of questions and that doesn't always happen.

DR. SOULE: Yes, and I think that is one of the intentions of really highlighting this patient counseling section, to put in a concise place for physicians and healthcare providers to see here is kind of a highlight of the things that you do want

to make sure your patient is aware of. Then, as we write the patient packaging inserts we do also make an effort to make them more readable, to have them at a lower reading level perhaps than the package insert might be.

MS. SHANKLIN-SELBY: I have to go on line to get a lot of the information that I want. I don't necessarily get it from the doctor or even the pharmacist. I mean, they are also supposed to be counseling, aren't they? Sometimes I will get a nice little brochure from the pharmacist but that is kind of stapled in there and by the time you have gotten your prescription you have torn everything apart. I don't think the communication has been particularly great from physician or pharmacist to patient.

DR. LOCKWOOD: Dr. Scott?

DR. SCOTT: Yes, this is little bit of a peripheral issue but just to clarify for myself, the FDA doesn't approve pre-advertising ads, either direct-to-consumer or in journals, or anything else. Is that true? Or is it just if something is

brought up that isn't true in the ad? Exactly how does that work?

DR. SOULE: There are very few situations-Bmaybe Dr. Monroe wants to address specifics, but very few situations where that is a required thing. Some companies do voluntarily provide and request pre-airing reviews.

DR. SCOTT: So, if there is an error in the ad that comes to your attention, the only way is if somebody complains about it?

DR. MONROE: Well, it is complicated and I don't want to be quoted because there is a separate group at the agency that does that. It is not a review division. There is a group that scrutinizes all advertising. In some circumstances, ads have to be pre-approved for certain drugs that fall into certain categories; for others they are approved concurrently.

I don't think any of us that are here right now want to give you an answer because we might not give you the right answer. We certainly could find that out for you and refer you to

whoever does that. But, again, there are different criteria for different types of drugs.

DR. LOCKWOOD: Let's move to the questions. The first question is can labeling information be made more useful for counseling patients to better inform patients about the likely effectiveness, safety, and other acceptability considerations, for example, that reduction in scheduled bleeding or unscheduled bleeding may be offset by an increase in unscheduled bleeding, whatever bleeding.

[Several member committee reply "yes"]

Yes? I think that is the consensus of the group.

Would such information likely reduce discontinuation rates and improve actual product effectiveness?

[Several committee members reply "maybe"]

DR. BUSTILLO: I think if the physician says it to the patient. I am not sure that just putting it in an insert is going to help you.

DR. LOCKWOOD: Right.

DR. JOHNSON: I was going to bring up a

topic. I think that Elizabeth made a good point that it would be nice to get information that the FDA put together for physicians for counseling, but also that can be handed to patients that is readable and usable because most of what we get, unfortunately, comes from the company that produces this product so there is inherent concern on patients' part of bias. So, it would be nice to have a piece of information that we can actually hand to patients.

Actually, most of the materials that come from pharmaceutical companiesB-I mean, they are done for marketing reasons and to be able to hand people a sheet that would be useful I think would be very helpful, and that is not so difficult to read. Is it reasonable to ask the FDA to do that, as well as to help with physician counseling?

DR. SOULE: I don't know if you are familiar with the patient package inserts that we do currently put out. Those are reviewed, again, by several different divisions within FDA. I guess what I am hearing you say is you feel that those

are not sufficiently accessible to patients.

DR. JOHNSON: They come with the product?

DR. SOULE: Yes.

DR. JOHNSON: It would be useful to have them available separate from the product, in advance of the product. Do you agree? On line?

MS. SHANKLIN-SELBY: Yes.

DR. MONROE: I believe that for contraceptives we have a brief and a detailed patient package insert that applies to all the contraceptive products. I believe those are on companies' websites. Usually when you go to a company's website they have information for a patient and information for a consumer. I believe that particular document does get posted verbatim now.

Admittedly, there is lots of other advertising probably as well but we can only control certain things, and we can control the physician labeling and the companion part of labeling that is designated to go to the consumer.

Both of those are a document that is

created both with the agency and the company. But for all oral contraceptives, they are relatively standardized, with the specific information as it relates to that particular product. So, they do contain a lot of what we call class labeling. So, unless there is a specific distinguishing characteristic which a product has demonstrated either in its favor or disadvantage there is great consistency amongst the products.

Obviously, how one would take a user product that is not an oral product, that has different dosing directions and so on, but for the most part we try to be consistent and we try not to make any one more advantageous than the other, unless there are true data that would support that.

Similarly, in terms of putting a warning in, we again try toB-I think everything we put in the label is based on data. The level of data and whether you agree with the interpretation of the data I think is maybe more of an issue, and the clinical significance of the interpretation of the data, but when we introduce warnings, particularly

of a bolded nature, it is based on information that we believe clearly justifies whatever the wording says.

DR. GILLIAM: I do know there is the study that shows that counseling about bleeding expectations with progestin-only methods does improve compliance, but I think there are serious limitations to our knowledge about the relationship between counseling and the greater public health issue of unintended pregnancies. So, I would be careful about answering 30b with a yes.

DR. LOCKWOOD: Dr. Hillard.

DR. HILLARD: With regard to class labeling, I think there are concerns about class labeling with contraceptives because the class labeling applies to both estrogen/progestin methods as well as progestin-only methods. Some of the information that is contained within class labeling based on evidence does not apply, at least to the same extent, with progestin-only methods.

So, I do raise a question that is of serious concern to clinicians and my colleagues in

other disciplines who get out the PDR and read about progestin-only methods, and look at contraindications that apply to estrogen-containing methods.

DR. LOCKWOOD: That is actually one of my pet peeves as well. Dr. Berenson?

DR. BERENSON: It seems that this committee has been pretty consistent on feeling that we need better studies on effectiveness. So, it seems that those same criteria should be used before warning boxes or bold-faced lettering is used on the product labeling as well. that we need good studies, not just anecdotal reports.

DR. LOCKWOOD: There is a tension that has to exist between protecting the public and ensuring that there is the greatest variety and acceptability of contraceptive agents available. I think that we, as a committee, probably can't provide a whole lot of insight into what the threshold is for black box warnings because there are just so many potential threats to the public health. I mean, it may be that we discover a

certain progestin, if used in combination with Tylenol, creates cyanide-Byou know, I am making this up! Well, you don't need a large randomized clinical trial to warn people that if you take more than three Tylenol while you are on this agent you are going to die.

So, I think they hear the message. It shouldn't be trivial. But I don't think we can require randomized clinical trials, or even very good observational trials, if the public health is imperiled by some sudden new information that comes to their attention. Dr. Blumenthal?

DR. BLUMENTHAL: Yes, I think, in looking at 30a and 30b and even to a certain extent jumping ahead to 31, and looking back at some of the literature that we were provided as background materials one of the things that decreases continuation is uncertainty or insecurity about how well it is going to work.

We have had some discussion before about putting effectiveness data in the label. I think that it should be displayed clearly in a manner

that both patients and clinicians can understand. Whether that means you just put a number or, perhaps even more advisedly, put a table in there that shows this method and sort of "you are here."

[Laughter]

You know, you are here in the range of all the other methods and options, or even going back to the WHO principle, if you had these classifications and you said, okay, here is the range of methods and, again, "you are here," this method is here on this continuum, I think that would be very helpful for people to put in perspective. Whether it is in the counseling section, and I think it should be in the highlights, myself. I think that information should be in the highlights. And, I would like to know if that is the plan.

DR. SOULE: Yes, and I should just clarify that the patient counseling section is one of the highlight sections that will be in shortened version, but yes. So, I don't know that we would be able to put a whole graphic table in highlights.

Probably space would preclude that but there might be some way of conveying some sort of textual message of that nature.

DR. LOCKWOOD: Let's tackle 31, which is the thorniest question. Should product labeling be modified to include pregnancy rates or safety data, such that there is, for specific subgroups when available? Universal consensus.

DR. TOBERT: I think it is very important--in general I am supportive of that, but I think it is very important that subgroups be predefined. It is only too easy to do data dredging and pick out particular subgroups which look bad or good, and that can be very misleading.

DR. GILLEN: Effectively, ditto. I mean, the thing that I am worried about there is just misinterpretation of the subgroup results where you are just kind of--if you have a priori specified some of these subgroups and you have good biological mechanism as to why things should be presented, then fine. But otherwise, you know, you could go through your data and find the green-eyed

person born on the third Tuesday of the month that suffers some adverse event.

DR. TOBERT: Just to follow-up, and you probably agree with this, I think there should be formal heterogeneity testing as opposed to just pulling out a number which looks bigger or, you know, is more adverse than the others.

DR. LOCKWOOD: The point to be made is yes, I think, but that subgroup analysis should have a biologically plausible rationale. Studies should be well conducted, adequately powered, and so forth, and it shouldn't be, you know, the result of the thirtieth subanalysis of some relatively small cohort. Dr. Berenson?

DR. BERENSON: And you have to know what you are comparing it to because we have talked about that we are using historical controls and that many of these studies did not use broad range of subjects. So, if we look at some subgroup, it may look markedly different than what we are used to seeing but is really not that different from if you looked at a wide population of a drug on the

market.

DR. LOCKWOOD: I think we are talking about active controls here.

DR. KAMMERMAN: I just want to point out that rulesB-I always get rules and regulations mixed up but somewhere, in one of those, companies and the FDA are required to look at subgroups to find by ethnicity, gender and age. Obviously, gender wouldn't be an issue here. And, there is a guidance on what to include in the clinical trials section of labeling and it discusses those particular subgroups.

What would be helpful to me is if you could provide some other subgroups that might be of interest, for example, defined by BMI subgroups or some others. So, if you could identify some of those, that would be helpful.

DR. LOCKWOOD: I think we would all agree with BMI, certainly BMI greater than 30, and you could have some flexibility as to the exact cutoff. But I think that, clearly we would. I would add first-degree relative with a history of venous

thromboembolism.

DR. SCOTT: But, Charlie, there are a lot of controversial or possible contraindications-Bdiabetics and certain diseases like lupus, and so on. I don't know if you are talking about including all those sorts of subgroups too or not. DR. LOCKWOOD: I think that there is actually some debate about diabetes. There is some debate about all those categories. Lupus now looks like they should be on oral contraceptives. But I don't think there is much debate about the risks with a first-degree relative.

Your mother and sister had pulmonary emboli, should you be on an estrogen-containing contraceptive? I would say unless you know that she doesn't have an inherent thrombophilia the answer is absolutely no. Even if she doesn't have an inherent thrombophilia and she weighs, you know, 300 lbs. and is 4'11" the answer is still no.

But ultimately that is the doctor's decision and there may be certain circumstances

where I would say yes to that. But I think the data where there are really robust odds ratios of risk, hazard risk, whatever statistical parameter you want to employ, where there is overwhelming evidence of added risk, and that is what we are talking about here, then I think it probably should go on the label but not for diabetes and lupus and things where, first of all, it doesn't look like there is any risk and, second of all, there is a lot of controversy. Dr. Stadel?

DR. STADEL: There has been a lot of controversy over the years about the question of subgroups in cancer and oral contraceptives. I would just reflect that there needs to be replicability of findings between independently conducted studies and a good appraisal and consensus development of findings before one moves forward with subgroups on some of these topics. Thanks.

DR. LOCKWOOD: We would all agree with that.

Next question, how can labeling best

communicate how to manage a situation where a patient misses pills? Oh, okay. I am out of date. How do we communicate the risk of an unplanned pregnancy in the days or weeks immediately following discontinuation of a product? So, after the treatment period ends.

DR. TRUSSELL: I think it should be clearly stated that if you stop using the product you are at high risk of pregnancy.

DR. JOHNSON: It is interesting because that is really what patients want to know. As soon as you stop them, your risk goes up and it goes up whenever you are off of them. So, I think maybe making that statement, where it is clear to patients, that they don't cause infertility and when you stop them your chance of pregnancy is high.

DR. LOCKWOOD: Consensus? Consensus. Okay.

Now, how can labeling best communicate how to manage a situation where a patient misses pills?

DR. TRUSSELL: This is an area that the

World Health Organization just spent an immense amount of time on and have issued guidelines in selected practice recommendations. Rather than reinvent the wheel, I would suggest that the FDA adopt them. It might be stated by some that these are too complicated but there is empirical evidence from studies about whether women understand them in the U.K. that led the faculty of Family Planning and Reproductive Health in the United Kingdom to adopt these regulations, and I do not believe that women in the United States are any less capable of understanding them than would be women in the United States [sic].

DR. LOCKWOOD: So, is that agreed?

DR. BLUMENTHAL: I don't think we should spend a lot of time reinventing what WHO has spent a lot of time, with a very similar group of people, to consider and improve.

DR. LOCKWOOD: Last question, should potential secondary, non-contraceptive benefits of hormonal contraceptives be discussed in labeling? Dr. Stadel and then Dr. Petitti.

DR. STADEL: I am concerned about the word "potential." I would say one would need to limit to things that are well established--this is usually in the observational literature--but well established, replicated from numerous studies, and if it is put in the label that it includes consideration of the dosing changes over the years that I mentioned earlier. But potential, no. There are lots of potential things and we need things that are fairly well established.

DR. PETITTI: I want to expand the discussion and my comment to question 31. I do think in this era of evidence-based medicine that the FDA should become more transparent and explicit in the standards that it uses for weighing evidence and for including things on the labeling. I do think that one could argue that there are methods available and approaches that would permit one to be very consistent in the decision about whether something is listed on the label as a contraindication, an established safety risk or an established benefit. This could be criteria that

could apply across a variety of products.

I do think that the contraceptive label includes a lot of sort of ancient and archaic anecdote both about the non-contraceptive benefits, which may or may not apply to the newer products, and have been kind of memorialized in this static document that becomes class labeling, and never changes and that a similar thing has probably happened even in the area of the safety issues where some of the prescribing patterns of the early use of the pill have clearly contributed to the very high risks of vascular disease that were seen in women in that era. For example, putting women who had hypertension on treatment, on very high-dose pills, is almost certainly one of the reasons why stroke was such a huge problem in the early products.

So, this is a plea to the agency. Maybe this could be the first case. The standards of evidence for contraindication subgroups defined as having higher risks and non-contraceptive benefits should be explicit standards of evidence.

DR. LOCKWOOD: And what standard of evidence would you apply it in? Level 1, level 2a, level 2b? A U.S. public health rating?

DR. PETITTI: I don't think it matters which rating system one uses to evaluate evidence as long as it is explicit and transparent, and that is based on a systematic review of the evidence and some kind of expert opinion. I don't care which one you use but use one and tell us what it is.

DR. LOCKWOOD: Dr. Peterson?

DR. PETERSON: Along those lines, one step further, one is going to have to decide with a body of evidence--once those are clear and explicit, which mostly addresses the non-contraceptive effects for the higher-dose preparations is that how do you handle the absence of evidence? So you can make the assumption that, because these are well demonstrated by these predetermined criteria for the higher dose preparations, that they would likely apply in the absence of evidence to the newer formulations.

The other approach is to say that you

assume that they don't apply unless there is evidence with the newer preparations, and the decision there is critical because there is an absence of evidence for the most part about the non-contraceptive benefits, prevention of ovarian and endometrial cancer. I mean 30-35 are studies but for 20s there is far less evidence to support that.

So, the question would be do you give that claim, or do you give that benefit presumptively, or do you say that we have to have the same standard of evidence as if it were a fresh, new thing?

The other is the issue of evidence of absence of an effect, which we have for example for protection against ovarian cyst. So, there is now some evidence that certain preparations do not protect. So, it creates a whole new set of challenges to do that.

DR. BLUMENTHAL: I actually have two questions for the agency which relate our question number 34. That is, let's say that a product is

put on the market and no studies are available concerning secondary non-contraceptive benefits. Then studies appear which demonstrate such benefits. Does the company have to apply for a label change, even if they are not asking for an indication but just to change the label so that this can be mentioned in whatever section is deemed appropriate? So, how does a label change come about in this setting?

The other question I really want to ask because something was mentioned in one of the talks earlier is with respect to start of the contraceptive. The Sunday start of the first-day start or a quick start, is that submitted to the agency by industry and you either accept or modify? Or, can the agency insert information about best evidence relating to the start of any 28-day cycle combined contraceptive?

DR. SOULE: I am going to take the second one first because I think that is a little easier. Typically, the sponsor initially proposes labeling to us and we then work and negotiate with them as

to what is acceptable.

DR. LOCKWOOD: So, and I don't know if this is actually reported, but would you say that this very low-dose oral contraceptive has an efficacy of blank based on quick starts as opposed to Sunday starts? Because there is some evidence of differential efficacy. Do you get to that level of detail?

DR. SOULE: I am going to turn to some of my colleagues who have done more reviews of these than I have. I am not aware of making those distinctions.

DR. MONROE: Well, generally the label ideally should reflect the way the clinical trials were done. If you have explored quick starts and the agency has accepted that as the protocol, then presumably our label should reflect what the clinical trial actually showed. I don't think we have any labels that talk about quick starts because I don't think anyone has proposed that to us, other than certain investigators that have been doing those studies.

There is some thought that if a study has been conducted only with, let's say, day-one starts, should we also allow the concept of Sunday starts? I think that has been sort of sufficiently well established that we have allowed that kind of exchange, perhaps in the absence of data, but the concept of quick start would be very different. Obviously, there would be different issues that might come up and you would have to provide the data to show that it worked as claimed, and, if you provided those data, it would certainly be reviewed and considered.

DR. LOCKWOOD: Dr. Berenson?

DR. BERENSON: This is a follow-up on Dr. Peterson's question. If you do put non-contraceptive benefits of a mono-contraceptive on a certain pill-Blet's just say dysmenorrhea, and one particular pill was labeled for dysmenorrhea--what do you do about other similar pills? Do they apply independently, each manufacturer? Must they do their own trials?

DR. SOULE: Yes, we have typically asked

for a secondary indication like that to be supported with clinical-trial evidence.

DR. BERENSON: By each manufacturer?

DR. MONROE: Well, that is in class labeling right now. I mean, there is this generic statement going back to the old--I mean, there are about six items, though I don't recall the exact number. You raise a good point. As we move down to lower doses, should those be included in that label because the benefits, which, I think, are based on a large extent on epidemiologic type data--and you folks know that better than I--probably there aren't a body of data that say the lower-dose ones convey the same benefit. Those are some things that we are independently considering, whether that whole section should remain, should not remain. That is all I am saying.

So, it is something that we are looking at right now. But if you wanted a specific claim that distinguished your product from another product, then you obviously would have to demonstrate it

with your product. So, there are very few things that we have awarded to drugs, other than some things that really come to us today from historical precedent in labeling, and some of this certainly needs to be readdressed. We call it class label, but based on data from different doses. That is what we are trying to say.

DR. KAMMERMAN: I always wanted to be in show business and I just lost my chance, but as a statistical reviewer and as a statistician I would have to answer no to number 34. The emphasis is on the word "potential." Anything that is in labeling can be considered a claim and can be used in advertising. To establish a claim the level of evidence is what we have discussed, usually two adequate and well-controlled studies with comparator where the effect can be attributed to the product under study.

So, if this happens, a potentional claim--I am not sure what that really meant--but if as a result of some secondary analysis the company happens to discover, or we happen to discover some

important effect, potential effect on acne, for example, then we would still require some additional studies. That finding would just be considered exploratory and would not be appropriate for labeling.

DR. LOCKWOOD: Let me just understand something. First of all, I think we all agree "potential" should be deleted from that question. So, we are talking about bona fide, documented, well-controlled trials, etc. Can you incorporate into the labeling evidence of secondary benefit that is based on outstanding data but hasn't gone through the rigor of a specific sponsored trial for that indication?

DR. MONROE: Other than the category of items which have been there as part of class labeling, we don't have any other benefits listed and for getting another benefit or claim, as Dr. Kammerman has just stated to you, sponsors have had to conduct adequate and well-controlled trials to get them. So, products come out usually as secondary indications. So, we do have some

products with acne claims and one with a PMDD claim, and those are all based on well-conducted clinical trials.

So, I would really interpret that final question perhaps really as more related to what Dr. Peterson brought up. Should we continue to carry those benefits that go back to class labeling which were based on epidemiologic data with higher doses, and do they translate to the present lower doses and even if we get down with lower doses or not? That is really I think what we were trying to get from you by giving you that particular question.

DR. LOCKWOOD: No, until proven, and when it becomes sort of a new class indication, that low ethinyl-estradiol-containing contraceptives reduce the risk of ovarian cancer and this has been shown in, you know, 15 well-controlled observational studies, and so forth. Dr. Espey?

DR. ESPEY: This getting back to what Diana was talking about. Does the FDA have any plans to change the process or the mechanism by which the label is changed? I am reviewing right now a paper

on an intrauterine device that shall remain nameless that recently underwent a package label change. It was updated from the prior label, which was 20 years old, and I think what is described in this paper is this incredibly cumbersome, expensive, difficult process in updating the label, clearly based on, you know, good quality evidence. I think Diana was referring to a lot of the same sort of anecdote, and that sort of thing, in the pill label. Will companies have just a major disincentive to update those labels because of the process?

DR. MONROE: Well, actually a while back, and it is a work in progress, the division did circulate a draft labeling change. Now, it is not based on the new format; it was based on the old format for labeling for hormonal contraceptive products. That did circulate. It did go out for public comment.

Now, probably most of you at the table are not aware of how this works. So, for a product that we have a class-label component for, as well

as an individual, and we make a change it usually goes out to a large audience, and it is published I believe in the Federal Register. So, the public is actually asked to comment on it, and it was circulated. Comments have come back and we are in the process of reviewing the public comments as to what areas they liked in the change, what areas they didn't like in the change and why.

So, there are different degrees of complexity of changing it. If it is product specific that doesn't have a large class component, that is one degree of complexity. But to change a label that has a broad class component, it is usually a complex process and it is not done usually just by the division. We circulate it out for public comment.

So, once that label is circulated--based on sort of lack of recognition on most of the faces, I guess none of you are really aware or had really commented upon it. But that is the process. So, all of this is codified in different ways, and they aren't things that we just do arbitrarily. A

lot of thought and effort does go into these things, although you may not always recognize that by our final product.

DR. LOCKWOOD: Dr. Tobert?

DR. TOBERT: I think there was an earlier comment to the effect that you needed better evidence for benefit and for harm. In general I would agree with that, with one exception. I think if the class labeling part of the label is going to be modified it certainly wouldn't be fair to retain the labeling about the small increase in breast cancer within five years or ten years, whatever it is, but discard the beneficial effects on carcinoma of the ovary and of the endometrium. There should be symmetry.

DR. LOCKWOOD: I think that is an important point. I mean, if you are going to delete the potential benefit for ovarian cancer that is ascribed to the higher dose agents, then do you also delete the evidence that there might be an incredibly small increased risk of breast cancer also attributable to the higher agent? I think the

answer is yes if there is no evidence.

DR. TRUSSELL: I would favor not eliminating it altogether because there is evidence of some sort so it is a potential of a different degree. What I would favor doing is saying that studies at higher-dose formulations, and you can list what formulations they are, have shown these benefits. Whether these benefits would apply to lower-dose formulations is not known. That is providing some information but it is not making a claim.

DR. LOCKWOOD: Dr. Blumenthal?

DR. BLUMENTHAL: Well, first of all, I am not sure whether you misunderstood the question that was being asked us a minute ago or whether I misunderstood your response, but I think with respect to changes in the label there are two components.

One is a change in the components of the label, so, what kinds of things are specified in the label along the lines of what Lisa told us in terms of the new type of label. So, the process

for changing the components of the label appeared to me to be what you were talking about a minute ago.

But I think some of the questions coming from the committee have been relating to what is the process for changing the information that is provided in a label, if that information should change for a specific product. There is a difference and I don't know what the process is and that is what I was asking before as well.

Similarly, Abbey had asked, let's say you had a product that did demonstrate an effect for a certain secondary benefit and there were a number of other products with identical formulations on the market, would the benefit that might now be inserted in the label accrue to those other identical formulations as well?

DR. LOCKWOOD: Yes, does it become class labeling? Do you change the class?

DR. SHAMES: Can I answer that? I think there is, I guess, some misinformation. Generally speaking, the company owns the label. We cannot

dictate generally what is in the label. There are certain times where we have more power to get our views on the label than others. Therefore, the process to change a label generally comes from the company for specific individual information.

So, they send in what they want in the label and, if it requires evidence, then they also send in the evidence. We review that and then we come to some kind of accommodation about what it should be. If we really don't like it at all we won't approve it. But, you know, generally we have to come to some kind of agreement because that is what the current regulations are.

DR. LOCKWOOD: But I think we are talking about two different things. I think that Abbey and Dr. Blumenthal were talking about changing the class labeling description, not the specific drugs.

DR. SHAMES: In terms of class labeling, we would have toB-see, in this case, you are talking about high dose versus lower dose, which might be more complicated.

DR. LOCKWOOD: For example, we have just

confirmed the lower dose.

DR. SHAMES: Let me just tell you some of the problems. The marketing is dictated by the label. Okay? I am just telling you some of these things that we deal with. So, whatever we change from one sponsor to another sponsor within a class might, in the view of some people, disadvantage their marketing which, you say, well, who cares about that?

Well, the thing is that then we have to convince the particular person or the particular company why we are taking this benefit out of their label and we have to have certain reasons for it. But we are looking into issuing new, as we did, labeling guidances and we can move to change it. But that kind of thing, dealing with class labeling, is a fairly cumbersome, difficult process when you are dealing with many sponsors. So, it is not as easy as it might appear just to go ahead and remove it. We don't have completely that authority.

DR. LOCKWOOD: Dr. Espey?

DR. ESPEY: Maybe I wasn't clear but my question referred to either a change in class labeling or a change in individual labeling, but let's just say the individual labeling like the IUD label change. I think a lot of those changes apply to both IUDs that are currently on the market but only one of the companies actually applied to get the label updated. But I was referring--I mean, we keep talking about how important it is to keep labels up to date but my understanding is that it is a very cumbersome and expensive process that a lot of companies would not invest in, even if the label changes are important and the old information on the label is really outdated, just because of the process.

DR. SHAMES: If you are talking about change, I would have to know specifically, not specifically with this product, but what kind of thing. If they are changing some important efficacy or safety information that requires data, they submit the data and we have generally about six months to look at this and decide whether it

should go in.

If you are saying we don't need to look at the data, we are not going to do that. I mean, in terms of cumbersome, they do have to accumulate data. If they want to make some kind of claim or change the claim, they have to present data, which may be in their view cumbersome.

The other thing is it is specific to the product. If they want to change the indication of one, as Scott has said, or say for an IUD, they were making some special claim, it wouldn't apply to all IUDs generally. It would apply to the one that was done in the trials. So, I don't know if that answers the question.

DR. LOCKWOOD: Dr. Petitti?

DR. PETITTI: This specific example might help. There is an oral contraceptive product where studies were conducted to show that use of the product, compared with the placebo, decreased the likelihood of acne. In fact, oral contraceptives are not labeled--the product labeling for combined oral contraceptives does not include a decrease in

acne as one of the secondary non-contraceptive benefits. However, a careful review of the evidence, which is substantial, would suggest that acne is a class benefit.

Now, as I understand it, the company that applied for a secondary indication of acne prevention or treatment could put that on their drug-specific label and that would not affect the labeling, either the class labeling or the product labeling, of any other contraceptive, including a contraceptive that had an identical pharmacological formulation.

So, the match between evidence of the non-contraceptive benefits and class labeling is not very good, nor is the match between the safety data in subgroups very good for the products that we currently are using because most of it derives from the era of higher-dose pills and more women in whom there were interacting effects.

DR. LOCKWOOD: Dr. Tobert?

DR. TOBERT: Yes, responding to Dr. Petitti, I think there is always a balance that has

to be struck between how much class labeling you allow when it implies benefit because you don't want to discourage new applications from actually doing good studies. For example, in the cardiovascular field, even though several statins have demonstrated a reduction in cardiovascular events, the FDA wouldn't, or hasn't hitherto allowed that as class labeling simply because it would destroy the incentive for anybody to do any more studies like that.

So, I think there is a tradeoff. Which side of the line acne falls on, I don't know but I certainly think if somebody wants to claim a reduction in, say, menstrual migraine they should do the trials and then they will get the indication.

DR. LOCKWOOD: Dr. Berenson?

DR. BERENSON: Correct me if I am wrong, but they could not have put class labeling in that particular instance because that was a patented formulation, and any company that was going after a new label would only do it for one that was under

patent because to do otherwise would not make sense from a marketing perspective.

DR. LOCKWOOD: Any other questions, comments?

DR. BLUMENTHAL: Is this like any new business?

DR. LOCKWOOD: Any new business, exactly. Dr. Blumenthal?

DR. BLUMENTHAL: Yesterday when we were discussing a lot of the study-design issues, and mostly methodologic issues, one of the things we didn't touch on, and it is certainly the purview of the discussion today to really discuss it in any detail, but one of the things we didn't discuss was what kinds of clinical data are required for the approval of a contraceptive in terms of the kinds of tests that a subject might have to undergo in order to be in the trial.

For example, a lot of things that we do and have been accustomed to doing clinically have no real merit in practice and probably don't have any merit in the approval of a contraceptive

device. Some of those kinds of barriers--those barriers to practice and they might be barriers to get into a clinical trial--have been studied by WHO, and also promulgated by USAID. So, at some point I think that the agency should review the kinds of clinical data it requires of industry or of an applicant for getting a contraceptive approved because some of the things we are asked to do as clinicians in a trial don't make any sense, and often unnecessarily exclude women from trials.

DR. MONROE: Would you elaborate specifically since you do have some things in mind, to make sure we understand what you are referring to?

DR. BLUMENTHAL: Well, the first one that comes to mind is the PAP smear. You know, these are contraceptives and while we can all recognize the value of cervical cancer screening at some point in a woman's life, if you were to have 16- or 18-year olds start to enter contraceptive trials, the caveat that you must have a normal PAP smear in order to get in a trial has no clinical meaning in

terms of a risk of cervical cancer, and no meaning in terms of the state of her cervix.

So to exclude them--and, in addition, as a result of being in a trial, they could then be exposed to all kinds of subsequent confirmatory testing, which is probably unindicated and has its own side effects. That is just one example. So, looking at the kinds of tests that one requires of industry to provide as part of an application is probably indicated now.

DR. LOCKWOOD: Does the FDA have any other questions they want us to consider? Thoughts? Comments? Dr. Slaughter?

DR. SLAUGHTER: I can do it after the break if you would like.

DR. LOCKWOOD: No, no, there is no break. Adjournment is coming up. Right?

DR. SLAUGHTER: I am probably going to beat this ad nauseam but I want to go back to your summary of 15 where you summarized to say that you weren't recommending a cutoff but, pretty much, you want to leave it to judgment relative to the

scenario for potential benefits, discuss the efficacy, whatever value you apply to a delta to be relative to potential benefits that the drug may have.

I am just wondering if you really meant the word "potential" or if we are really talking about something supported by evidence. If so, what level of evidence are we talking about?

DR. LOCKWOOD: I think I can speak for the group. I think we very much meant potential, that there could then be Phase 4 studies that confirmed, with excellent data, the potential benefit that drove the decision, and they could then seek a new indication. I think it would be unfair and, in fact, impossible for some of these indications that will be generated to be doable in Phase 3 studies.

I will restate this. The committee refused to be pinned down to a specific upper confidence interval for efficacy because there are so many variables that ought to be taken into account when assessing a new sponsored agent, and so many potential side benefits which have

biological plausibility that we want the greatest possible latitude shown in demonstrable efficacy.

We gave you some very broad ranges of intervals that you can consider. But the key caveat is the word "depends." It depends on why the new agent is being brought to you. So, we want to encourage the availability of the broadest possible array of contraceptive options to women, and that means that ultimately the final decision on the suitability of an agent ought to be left to the doctor and the woman on the basis of the available data. If anybody else wants to modify that, feel free. Dr. Gillen?

DR. GILLEN: I would just like to add one thing. So, when deciding upon this non-inferiority margin or an acceptable non-inferiority margin, this is clearly a clinically subjective decision that one is making.

So, the question was, you know, you have this potential benefit so how low do you lower the bar effectively relative to what is out there? Well, personally, if it is not an established

benefit that I know. I am going to be much less willing to lower that bar for efficacy if I haven't actually established that this thing actually truly has some other benefit on a secondary endpoint. Because I can't know that. I can't possibly know that. So, why would I be willing to give up something on efficacy if I haven't actually established a benefit in some other secondary endpoint?

So, that is something else that needs to be taken into consideration each time these different non-inferiority margins are going to be set.

DR. LOCKWOOD: Dr. Trussell, do you want to make a comment?

DR. TRUSSELL: I thought that is what you said.

DR. LOCKWOOD: Yes, Dr. Peterson?

DR. PETERSON: I think that when we start getting into the realm of theory we can start arguing things a bunch of different ways. We could argue, for example, that a 10 mcg pill might not be

more safe; it might be less safe in terms of adding back for bone or something. So, if we start changing our thinking based on what might be, it creates a whole cascade of things that probably aren't good.

DR. LOCKWOOD: Dr. Stadel?

DR. STADEL: I think if the agency chooses to follow the direction of the committee with regard to comparative trials, the reality is it is going to have to ask the company to propose what is feasible and to negotiate that, and then you are going to have to look at that data and what you can actually get and consider it, perhaps along with data on other effects.

I was imprecise in using the word surrogate outcome for ovulation suppression. It is not a surrogate for pregnancy. I think it probably has some value for combined oral contraceptives. But I did want to make that correction. But you are going to have to look at what can be done. I mean, I don't think you can come up with no information in advance and set a limit.

DR. LOCKWOOD: Dr. Gillen provided a very nice framework for how to approach that from a statistical standpoint by analyzing literature, conducting meta-analyses, determining the approximate confidence intervals and then establishing a priori what the sponsor intends to prove in terms of fitting within that interval. I just summarized the very articulate statistical argument in an obstetrician's fashion.

At any rate, if there are no other comments, I move to adjourn.

DR. WATKINS: Thank you, all, for coming. I know this is a very difficult topic and you did a wonderful job.

[Whereupon, at 3:03 p.m. the proceedings were adjourned.]