followed in the SART registry.

But everything that we've been discussing here today really should be monitored.

DR. GREENE: I'd like to--Mike Greene.

I'd like to put in a plug for a couple of specific things. One is the issue of monozygotic twinning, which I mentioned earlier. Another is the incidence of premature delivery, regardless of the multiplicity of the gestation--even if it's just a singleton gestation.

I think that--I'll leave it to the FDA staff people to ponder the practicality of worrying about the incidence of cerebral palsy, because that poses a significant methodologic problem, in terms of long-term collection of data. And the other issue is the high order multiple gestation rate associated with a drug, or combination of drugs; and is there--would there be evidence that some drugs, or the way that they're commonly employed, lead to a higher incidence of high order multiple gestations than other drugs, or the way those drugs are employed?

DR. DATTEL: Bonnie Dattel.

Just also a plug in for treatment failures, and including women who have multiple cycles and fail, because they'll never get into the pregnancy registry. So--and, also, how many cycles someone has had and then has a successful pregnancy; how many times their ovaries and the

dormant ova have been exposed. So those, I think, are important.

CHAIRMAN AZZIZ: I think the biggest challenge--obviously that's why we're discussing it in the Committee, is how to differentiate, as Richard said--how to differentiate an ART-related procedure problem, versus a drug problem. And we are obviously here in the business of attempting to determine whether the drugs have an impact on pregnancy outcome, not--the rest of the FDA, perhaps, interest in looking at ART outcome.

So I am actually relatively loathe to increase the number of things that need to be monitored beyond that--what would be not monitored normally for other drugs. In fact, if anything, there should be, certainly, a caveat that perhaps many of the things that we might observe may actually be related to the embryo manipulation or ART procedure. So, in fact, I would tend to--other than a few specific items that are being brought up, I would actually suggest to the Division that they do not increase above what they already are going to look at for other drugs, and perhaps even then, take those and perhaps limit that.

DR. GREENE: Mike Greene. I had my button pushed, I guess.

I had one concern, and that is that although there's a different branch of the FDA to look at devices, I

wonder whether there are certain aspects of the ART that might not fall between the cracks. So, for example, if merely prolonging the period of embryo culture from two days to five days in and of itself could increase the incidence of problems, who regulates that? The people who look at the drugs, or the people who look at the devices?

DR. TRUSSELL: James Trussell.

I hear and understand the need for long-term follow-up, but I haven't heard anybody put a number on it. So are we talking about five years, 10 years, 20 years, 30 years--what is--it's a huge question. I mean, it's a very important question with huge implications.

CHAIRMAN AZZIZ: I think--Dr. Rarick, do have a clarification there, because there are other sections of the FDA looking at the device pregnancy outcome, or at least it's been--you've come up with some guidelines recently. So perhaps you can educate us.

DR. HOUN: The Center for Devices does have a post market surveillance office, and they, under the device statute, have a different requirement, where they can impose a requirement for such studies under specific serious conditions.

In terms of who governs how long an embryo stays in the culture dish, that is not under FDA regulation. That's under practice of medicine, and various guidelines

that exist in the medical world.

There could be a possibility, in terms of talking with the Center for Devices and the Center for Drugs, to try to figure out if there are some common types of devices that the Device Center has questions on, but they wanted of include in this effort. I mean we could investigate this further if this is something the Committee would like to get information on.

CHAIRMAN AZZIZ: But the FDA actually has had some guidelines recently, regarding the manipulation of embryos and of gametes and, in fact, I may have to ask Shawn from ASRM to speak on that--and the public--just so that--for our Committee's information, would you mind saying a word Shawn?

MR. TIPTON: Right now?

CHAIRMAN AZZIZ: Yes, sir.

MR. TIPTON: I'm Shawn Tipton, I'm the Director of Public Affairs with the American Society for Reproductive Medicine. There are a couple things, I think, that might come into play. One is the device folks have actually recently backed off a little bit of having some special consideration for ART devices, and so we're going to treat these the same as we do devices in other fields.

What Dr. Azziz, I think, is referring to is the--a proposal out of CBER to--it's more sort of tissue, culture and infectious disease prevention guidelines that have been

proposed; published the Register, I guess September 30th. So they are certainly moving that way. And again, I don't know to what extent--they certainly are talking about what's in the culture media. I don't think they're talking about how long it will be in there.

CHAIRMAN AZZIZ: Thank you. I wanted to bring you up, because I do know that CBER is working on some of the media, and aspect, and so on and so forth. So I think it's important.

But I'd like to, for the moment, concentrate on what we initially started out, which is ART pharmaceutical drugs, related to the process. And, again, my comment was: it's going to be very difficult to separate those, so I would not want to overburden the system just because I think we're going to get more confounding data.

DR. DATTEL: I just--Bonnie Dattel--I just had a comment on follow-up, and how long is "long," and I think we have to go back to the DES story, and that it may take a generation, if these are fetuses exposed to potent drugs affecting reproductive organs. We may not know the answer in three years, or at school age. There may be a sub-set of patients that need to be followed for longer than that. I don't know the answer to that.

But I think that we shouldn't cut ourselves off too soon, in terms of reproductive issues later for the

offspring.

DR. GREENE: Mike Greene.

I'd like to ask another point of clarification, and that is: is it necessary that there be a Phase 4, if you will, that must be completed prior to licensing? Or would that--would licensing be possible, and part of that licensing require a Phase 4 surveillance?

DR. RARICK: Yes, we wouldn't refer to it as "Phase 4" until after approval. People could certainly begin these things in Phase 3, prior to approval. So, for example, while a new drug application is being reviewed, they could already have put in place some follow-up of their patients in clinical trials, or start a new IND where they start a registry of users.

But in terms of our abilities to impose requirements at approval, we then call those "Phase 4 commitments." They are agreements with a sponsor to do things in Phase 4 that we then monitor.

CHAIRMAN AZZIZ: A question again--it was mentioned earlier that once you get into the generic issue it becomes very difficult to monitor these things. And perhaps you can tell us why.

DR. RARICK: I'll try. It's a simple--the simplest answer is just the finances and the feasibility. So, for example, if the innovator company--the initial

company--no longer is on patent, and they're no longer making money from their product, they're not particularly interested in continuing to run a very, very expensive pregnancy registry system, when a generic has taken over the market. And yet they are the innovator, and they would be the ones that it would initially imposed upon, because they have that three to five years exclusivity at the time of approval.

CHAIRMAN AZZIZ: So when a generic manufacturer comes on the market, that can't--I mean, you can't require that all the companies who are producing one product to do this? I mean, this is--maybe I'm just being foolhardy, but I just don't quite understand--if all of a sudden four companies are producing a gonadotropin, why can't you just have a collaborative--coordinated through the FDA? I'm not sure.

DR. KWEDER: It's actually extremely difficult. Generic manufacturers are not in--usually in the business of conducting research. There are usually more than one of them. They don't have R&D groups that innovator--we call them "innovator pharmaceutical firms," the ones who bring--do the actual development and bring a product to the NDA approval process--have. So it's--just the logistics is tough.

Now, if the FDA were coordinating something, or

had another carrot that it could offer, we might be able to do more, even with the innovator firm.

An example of that is that within the past few years in pediatrics, what we have been able to offer--and this is only because of a Congressional action--is we can offer an innovator company additional marketing--six months of additional marketing exclusivity for actually studying a pediatric indication that we think is important. And, you know, initially one might think, "Well, six months--what's the big deal," you know, when you have a marketing exclusivity for seven years. Well, six months is a big deal. It's a huge deal. It's billions of dollars. And we've had great success with this program, with companies' coming forward, because it carries to the entire molecular entity.

We don't have such a mechanism now for pregnancy registries, or long-term follow-up studies for drugs relevant to pregnancy outcomes. I think it's something that, you know, is certainly worth considering in the future, but it hasn't come before us yet.

Does that help? Does that answer your question a little bit?

DR. GREENE: Mike Greene.

Again, please correct me if I'm wrong, but I think part of the problem also is that a generic manufacturer may

not necessarily be incorporated in the United States and subject to American laws. Is that not true?

DR. LERNER: Just as a corollary with that--from what Dr. Kweder said is, I think, a labeling change, or a new indication, where you then give them more market exclusivity is certainly a perfect tie-in.

DR. RARICK: No, generic companies that are outside of the U.S. still meet our rules and laws. They still submit abbreviated new drug applications. I think Sandy's was to the point of--general applications don't include a clinical section, or a post marketing surveillance section. They are specifically copies of an innovator product, and they are--chemistry and manufacturing controls almost exclusively is what's in their packages.

Labeling is a route for giving an innovator a carrot, in terms of a new indication, but often times pregnancy information added to a label is not necessarily a new indication, and it never has been. It's simply been added information in a pregnancy section. Because the indication remains the same. It's for--let's say it's an anti-hypertensive. Simply because it's an anti-hypertensive in pregnancy, it's not usually a new indication. It's simply an anti-hypertensive.

DR. LERNER: No, I'm not saying a new indication in pregnancy, but I'm saying a new indication for whatever

their new indication is for--some new medical disease or entity that's,you know, completely unrelated, but they're sort of coming back to you and are beholden to you, so that may be, then, a good carrot to tie them in.

DR. RARICK: Oh, yes, it's always easiest to negotiate those Phase 4 agreements when you have an application that you're working on for any indication.

CHAIRMAN AZZIZ: I mean, obviously, we don't want to recommend something that's going to be overburdensome to a pharmaceutical company. We certainly want to foster drug innovation. So, again, we always have to keep that in mind as we recommend these issues. But, again, these drugs are highly related to reproduction and subsequent outcomes, so I think that that's an issue.

Further comments on number 3? If not, we'll summarize and move forward.

DR. TRUSSELL: It's a clarification, really, of what you meant when you summarized it before. But even though the focus here is on the drugs that are used, it would seem to me that a registry would be rather useless if it did not have information on all the stuff that was ancillary to that to get the woman pregnant in the first place.

So all of the devices that were used--blah, blah, blah, blah, blah--if you don't have it, it's going to be, in

my opinion, useless.

DR. WEISS: Sheila Weiss.

I want to add to that. I think there's two things we've been dancing around. Maybe they're dirty words. One is "collaborative," and the other is "comparative." And I think those are things that we need to think about when we're thinking about ART; that whatever data we collect, be it on drugs, on methodology, on devices that are used, we'd like it to be consistent from one study to another, and the follow-up be similar. Because one of the things you're going to want to do is say, "Well, is it the drug or the device, or the method?" And the only way you can do that is if you have comparative data--or another comparative population. And I think one registry, or a--that is comparable to another, or a collaboration that works together is the only way we would be able to do that.

CHAIRMAN AZZIZ: I think those are very valid concerns, I think.

Just as a reminder--the SART data does have the outcomes of all the pregnancies of women initiated in ART, and the drugs that they took during pregnancy. That drug data currently has not been collated or used. I mean, it is accumulated at the CDC right now. But, I mean, that data has been collected for the last four or five years now, so that that information is actually available, and could be

generated relatively quickly if somebody put a few resources to get somebody to collate through the data.

So that actually has already been obtained, and probably we already have enough information today from that database to answer most of these questions, other than absolutely new drugs; things like the antagonists, and so on and so forth.

DR. FALK: Just to make not of the fact that there's one other aspect of assisted reproductive technology that's gone unmentioned here, and that may be the crack that was referred to before--and that is that this is, in a way, a surgical procedure. So it's not just drugs, and it's not just devices either. It's also the people who are handling and manipulating the embryos. And that's why the SART data is particularly good in that regard, because it is clinic specific.

CHAIRMAN AZZIZ: Any further comments?

[No audible response.]

Let me just simply summarize. I think that the ART issue is confounded by the fact that obviously there are devices, laboratory procedures and surgical procedures involved here. Certainly, I think all of us would like to see long-term data in these drugs--not just the procedure, but in the drugs. I don't think, other than simply information related to the procedure specifics, I have to

agree with Dr. Trussell that it is worthless to use this data if you have no clue of what actually happened, or what procedure was undertaken. But, again, the issue has been that this data currently has been and is now obtained, and rests somewhere in some basement at the CDC; but that data has already been there so that, in fact, if the FDA wants to put some effort into looking at this data, that would not be a monumental task, other than paperwork.

Let's move on to question 4--3, I'm sorry.

One, what other mechanisms exist to collect this type of data or other information? I think we may have answered that already. Anybody want to add to that?

[No audible response.]

CHAIRMAN AZZIZ: Okay. Let's move on to 3(b): Does the Committee have any recommendations on how these or other mechanisms might be encouraged?

DR. LERNER: I just had a quick question. I know, with the NIH money drying up, perhaps including some of the other agencies, in terms of trying to establish some databases and some money from elsewhere might be a good idea.

CHAIRMAN AZZIZ: Something about "money talks and--"--

[Laughter.]

CHAIRMAN AZZIZ: All right.

DR. DATTEL: Bonnie Dattel.

I think we do have to encourage the societies that are working with these tools to participate in this, and provide the information--such as you've already mentioned, Ricardo--that is available, and to continue to do so, and--as part of their own process, if you will--I don't want to call it "monitoring process." But I think that I would encourage societies to continue to collect the data and participate in this research, in terms of collaborative effort.

CHAIRMAN AZZIZ: Just a reminder though--I mean, societies, unfortunately, are not in the business of doing that. In fact, societies are not--professional societies, most of them, are obviously not regulatory. So while SART has done something that I think is uniquely extraordinary for a non-profit society, I do think that it's probably not going to happen, as societies see membership dwindle, pretty much around the country--everybody is paying less, and so on and so forth. So I don't think that that's--I don't think that's the place.

I mean, clearly, the people who make the money on the process should be, obviously, the one's that have the vested interest. But I do think--like I said before--that that database is there, and certainly would be--with outside funds, could be probably studied. I don't know of any other

mechanisms, which is what we're trying to--do we have any other suggested mechanisms?

I think it would be foolhardy to try to repeat and reinvent that wheel. That wheel's undergone a lot of reinvention, and I think it's working okay.

Further comments on number 3?

[No audible response.]

CHAIRMAN AZZIZ: Okay.

Let's move on to number 4: are there any other comments or suggestions for the FDA on the two draft guidance documents discussed this morning, which are the Reviewer Guidance--Evaluation of Human Pregnancy Outcome Data, and Guidance for Industry--Establishing Pregnancy Registries--and, again, this refers to the text that you actually have.

Any worthwhile comments that you've noted on the side? And I think we've gone through some of those already, but perhaps if you have some, it would be very helpful.

DR. RARICK: Let me just note that if you have been editing it extensively, and have many, many written comments, you can give those to us, rather than reading them all completely here. But there's major general issues that you'd like for us to consider as a group, we can hear them now.

MS. HAUSER: I have a comment and a request--not

so much on the registries, but perhaps to Dr. Kweder and her group on pregnancy labeling. And I think she alluded to this--the problem of provider liability in interpreting the labeling, as far as using the medications and incurring risks related to a potential association, as well as the reverse problem.

And I looked at the list of members on that committee. I don't know if you had any representatives from the legal profession, which we're in constant professional tension with around these kinds of issues. It might be helpful, if there are no members, to have one or two perhaps as part of that.

CHAIRMAN AZZIZ: I have--in addition to the comments I made earlier about the, sort of, dichotomy, and some of the comments on the table that's needed and so on--in your page 11 of your first draft, it says, "Selection of Comparison Group"--that's a concise statement but it isn't very helpful.

I think that it needs to be a little clearer as to how and when is a comparison group going to have to be required. And that wasn't helpful to me and, in fact, I was trying to figure out how I would get a comparison group. So--

The second thing--I think Dr. Harris pointed out--and you're going to have to remind me--yes, the legal

issues of the provider. This is a different kind of plea, but I'm involved in the FDA, and I still sometimes have no clear idea of what the FDA's regulation over practice is. We know that it isn't there but, yet, for example, if I went to the Web site and tried to figure out where on the Web site does it say that practitioners can administer drugs above and beyond what the FDA approves--and I know Lisa FAXed me something one time--that's not easily available. And at some point the FDA's going to have to undergo some physician education programs relating to the FDA function. Because I can tell you this is the major mystery and bugaboo--for those of us who are here, much less the ones who are out in the practice.

DR. KWEDER: Yes, I absolutely agree. And I think that we are--we don't do that very well at all. You know, and in fact, I can remember--just as an anecdotal experience--being at a meeting--this illustrates this--while being at a meeting, where the discussion was the use of thrombolytic agents in ,pregnancy, and someone was talking about--low molecular weights heparins was the topic of discussion, and a woman who cares for a lot of pregnant women, who actually studies some of these in pregnancy, got up, and she said, "And--" --it was heartfelt; very frustrated--she said, "And we really think that these products are probably safer than regular heparin in

pregnancy, and the FDA won't let us use them."

And, you know--but I think that's--it's exactly what you're talking about. I think it's very misunderstood. We don't communicate it clearly. And we, ourselves--we know what we do [laughs]. Everybody else doesn't. So--well taken.

CHAIRMAN AZZIZ: Any further comments on number 4, here? If you have extensive editing things, please do hand them to the staff. That will be very helpful to them. But other comments on the two draft documents? They were very clearly written. I liked--I mean, whoever wrote them--nice writing. I just need to say.

But, in general--anybody else have any comments?

[No audible response.]

CHAIRMAN AZZIZ: All right. And since we are 15 minutes ahead of time, I don't think we'll have time to start on the afternoon schedule, but I would like to start earlier this afternoon than the time here.

Let us now break for lunch. Let us meet and start at 1:15. Thank you.

[Whereupon, the proceedings were recessed to be resumed at 1:15 p.m.]

A F T E R N O O N S E S S I O N

CHAIRMAN AZZIZ: Okay, let's go ahead and re-start, please. It is now 1:18. We'd like to stay on time. We have a lot of work to do this afternoon.

Again, I'd like to introduce Dr. Rarick, who is going to introduce our afternoon discussion.

DR. RARICK: And this will be quick--thank you, Ricardo. I forgot to mention this morning--congratulations to all the Mets fans out here. Yeah, we have one--and Atlanta--Atlanta, I know, you're depressed. It was a fund game last night.

Anyway--I was just going to bring us back from lunch--to change gears, we're going to be speaking about two guidance documents. They are guidance documents that currently exist and ar under revision. And Dr. Susan Allen will be describing each of those two us: Estrogen Class Labeling--both estrogen and combined estrogen/progestin drug development guidances.

Thanks, Susan.

DR. ALLEN: Can you hear me in the back? Yes? No? If I lean over, is that better? Okay.

Well, let me say welcome back from lunch. And I'll preface my talk by saying that over the last two weeks, every Sunday in the paper I looked through the comics to see if I could find some type of cartoon that would enable me to

lighten up this presentation that I'm going to give to you. But Garfield and Doonesbury were not too helpful in this regard. So I will do my best to make this interesting for you, if I can't make it totally entertaining.

And, as you can see here, the title of my presentation is: "FDA Guidance Documents related to Estrogen-Containing Drug Products--Current Issues and Status." And let me say that the bulk of my discussion will relate to documents that are contained in the latter half of your pre-meeting packet. So that's section 3(a), 3(b) and 4. And I will be presenting a great deal of information in a short period of time. But one thing I want you to keep in mind is that--as Lisa mentioned--nothing is set in stone. These are proposed revisions to these guidance documents, and we will certainly be seeking the opinion of the committee, as well as those of you in the audience, about the proposed changes.

Next slide, please.

I have three goals for my presentation. The first is to describe current guidance documents that are prepared by the Division of Reproductive and Urologic Drug Products, and are related to estrogen-containing drug products.

I'm going to review--briefly review--the content of two of these documents for you, and I will summarize proposed changes in two of these particular documents.

Next slide, please.

There are three guidance documents produced by our division that are related to estrogen-containing drug products. there are two labeling guidance documents and there is one drug-development guidance document. The two labeling guidance documents are, first, a Guidance Document for Non-Contraceptive Estrogen Drug Products--that is also known as "estrogen class labeling."

The second labeling guidance document is a guidance document for combined oral contraceptives.

The Single Drug Development guidance document that the division prepares is a guidance document on estrogen and estrogen/progestin-containing drug products for HRT in menopausal women.

Next slide.

The two that I will be focusing on today are the ones that you see there. I will talk about some proposed revisions in the Labeling Guidance for Non-Contraceptive Drug Products, and I will also talk about some revisions in the Drug Development guidance for clinical evaluation of estrogen and estrogen/progestin-containing drug products for HRT.

Okay. Let's start first with estrogen class labeling document, and let me begin with a bit of a background for you.

In Section 3(b) of your meeting packet, you will see a previous version of this document that was published in 1992. And I also want to let you know that this document was put out for public comment in the fall of 1998. The Division received extensive suggestions for revision in the document at that time. We did make some revisions to it, and we also made some changes based upon our internal thinking about the document. And that has resulted in the draft guidance that you see in Section 3(a) of your packet.

So what I'm going to be doing is talking about changes in the document, in Section 3(b), that have resulted in the document under Section 3(a) of your packet.

For the next few slides, let me talk about specific components of the guidance document originally produced in 1992 that have been proposed for revision. And the first section is the boxed "warning section" in that guidance document. If you look at the old version, you'll see that there were basically two issues that were covered in the boxed warning of that particular guidance document. One was the increased risk of endometrial carcinoma associated with unopposed estrogen use, and the second was the use of estrogens during pregnancy, with a particular emphasis on DES effects in male and female offspring of women who took that drug during pregnancy.

The pharmacology section of that document really

gave an extensive explanation of the mechanism of action and the metabolism of endogenous estrogens. It didn't focus a great deal on exogenous estrogen administration, or specific routes of administration of those types of estrogens.

Next slide, please.

You'll also see that in the older version of the guidance there were seven indications listed for which these drug products may be developed; five of them were specific for ERT--or estrogen replacement therapy products--and those five are: the treatment of moderate to severe vasomotor symptoms associated with the menopause; the treatment of vulvar and vaginal atrophy associated with the menopause; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology; and osteoporosis prevention.

Next slide, please.

You'll also notice that the older version of the document focused primarily on provider labeling, and there was a separate patient package insert guidance. As I mentioned a few minutes ago, because we did receive suggestions for extensive modification to this particular document, we decided to go ahead and publish again the draft revisions in September of 1999--so just a few weeks ago.

Okay--with regard to the proposed changes that the

Division is suggesting in this particular guidance document, overall you can tell that the new version combines prescribing information and information for patients in a single document. And even though there is mention of combination estrogen/progestin therapy in this guidance document, it focuses more on estrogen-alone drug products.

Now, the last item on this particular slide I want to emphasize for a minute. You can--if you've looked at the older version, compared it to the newer version, you'll see that the detailed information on the prevention and management of osteoporosis has been deleted in the proposed revision. That does not mean that the indication has been deleted. If you'll turn to page 6, item number 6 at the bottom of that page still lists the indication of prevention of osteoporosis as an indication for drug development of drugs in this class. Inadvertently--not intentionally--this particular indication was omitted from the patient labeling section of this document. So, hopefully, that clarifies some concerns that you may have in that regard.

Next slide, please.

With regard to changes in this particular guidance document, you'll see that the boxed warning in the newer version now is limited to a discussion of the increased risk of endometrial hyperplasia associated with unopposed estrogen use. The previous text that related to the use of

estrogens during pregnancy has been moved to the "precautions" section, and there's been an expanded discussion of that particular issue in that section.

The pharmacology section of the newer document now requests specific information for different dosage forms of these products. There's some discussion about oral estrogen-containing products; topical, or intravaginal dosage forms, as well as transdermal forms.

You'll also see that there's a request that sponsors provide detailed information on specific pharmacokinetic parameters about the drug product that would include such things as absorption, distribution, metabolism and excretion of the particular product. There's also a "special populations" subsection in the pharmacology section, and that was added to deal specifically with certain patient populations,such as those that may have renal or hepatic impairment and may require dosage adjustment during drug administration.

There's also a "drug interactions" section. And we added this specifically because there is a great deal of published literature now that discusses the impact of ethinyl estradiol--contained in oral contraceptives--and its metabolism, on other drug products, as well as the converse: the effect of other drug products on the metabolism of ethinyl estradiol. We don't know if other

estrogen-containing products react the same way, but we decided to include as much information as we had on this particular estrogen, which is ethinyl estradiol.

Next slide, please.

One of the bigger changes that I think we are proposing to make in the document is a change to require that the indication that winds up in a label for an approved product is specific for the trials conducted. If you, again, look back to the 1992 version of this document, you'll see that if a sponsor had conducted a trial demonstrating efficacy for one particular indication, the guidance document technically allowed them to include the other indications in their label, even though they really didn't do a clinical trial to look at those other indications. And from our perspective--and also thinking about how the public would gain the most benefit from information provided in a label--we felt that it was very important to now say: "You must conduct a clinical trial for each specific indication that you want approved," because it's only through that process that we will obtain meaningful dosing information to include in the label.

We're also proposing that the indication entitled "abnormal bleeding due to hormonal imbalance" be deleted from the new version of the document. We found this to be a very vague indication--but we will ask your opinion in that

regard.

Next slide, please.

We've also added several new sections and sub-sections to the document. We have a "Clinical Studies" section now that asks sponsors to describe the study design of their Phase 3 clinical trials, including end-points. We've added a section on hypothyroidism, for women who may possibly need an adjustment in their thyroid hormone replacement therapy if they're talking exogenous estrogens. We've added a venous thromboembolism sub-section in the "Warnings" section to describe the increased risk for this particular event in women who are current ERT users. And then we've added a pediatric and geriatrics use section, as required by the regulations.

You'll find some minor editorial changes throughout the document. And then, again, the latter half of the document is devoted to patient labeling that we hope conveyed the information that was contained in the first half of the document--or the provider labeling part.

Okay. That's one guidance document.

Now, what I'd like to do is spend the rest of my presentation time on the second guidance document, which is the ERT/HRT drug development guidance document.

Once again, as some background, this particular guidance document was first published in 1995, and it

focused on the combination of estrogen and progestin products for use in menopausal women. It was originally intended to describe recommendations for endometrial hyperplasia prevention studies, but if you look at it, it also appears to address several other things: the treatment of vasomotor symptoms; the treatment of other symptomatic indications; and also osteoporosis prevention.

Next slide, please.

Also, if you look at that document, I think that you will find that there's an enormous amount of information contained in it, but it's not well organized. So one of the first things that we're proposing to do is to get it organized, and to change the format so that there are two separate sections to this guidance document. The first section will be dedicated to estrogen replacement therapy, and the second will be dedicated to those trials looking at endometrial hyperplasia prevention.

Each section will contain information on the following items: the indications for which those drug products may be developed; the study design of the Phase 3 trials that are recommended or required; the inclusion criteria for those trials; study end-points; and also safety monitoring throughout the conduct of the trials.

Next slide, please.

Okay--so think in sections again. We're going to

talk first, now, about Section 1 of this guidance document, which will be devoted to trials of estrogen-containing drug products, or ERT trials.

Okay. You'll see that the current version of the guidance document lists five indications for which these products may be developed--very similar to what you saw in the estrogen class labeling. They are the treatment of vasomotor symptoms; vulvar and vaginal atrophy; hypoestrogenism due to hypogonadism, castration or primary ovarian failure; treatment of abnormal bleeding due to hormonal imbalance; and prevention of osteoporosis.

Next slide, please.

We are, once again, proposing to delete some of those indications that were listed on the previous slide from the newer version of this guidance document.

And, Lonnie, can you go back one slide, please?

And we're actually proposing to delete the latter three indications on this particular slide. And we will be asking the Committee's opinion, as well the opinion of those in the audience about that proposed action.

Next slide, please.

Did you skip one? You did. Okay.

Also, the proposed revisions in this section of the document really are going to focus on the vasomotor symptom indication. You'll look at the older section--the

older version of the document, and you see that it appears to address all of these different types of symptomatic indications, when really it's focusing on the vasomotor symptom indication. So we're going to appropriately title this section that way in the revised version.

Go ahead.

We have made some modifications in the number and the design of trials that will be needed for these particular drug products, and we've reduced the number of trials required from two to one. That single trial must meet all of the criteria that are listed on the bottom half of this slide. It must be placebo-controlled; it needs to be double-blind; it needs to be of at least three months' duration; and it needs to evaluate dosage levels, so that the lowest effective dose of the estrogen product can be determined.

Next slide, please.

With regard to inclusion criteria, the Division currently defines menopausal status in the following way: greater than or equal to 12 months of spontaneous amenorrhea; or greater than or equal to six months of amenorrhea, with an FSH greater than 40 million IUs per ml, and an estradiol less than 20 picograms per ml.

Next slide, please.

Women who choose toe enroll in these trials, and

who have been using estrogen or estrogen/progestin-containing products prior to enrollment should undergo wash-out periods before an assessment is made of vasomotor symptoms at baseline. And we suggest the following wash-out periods for each of the different types of products that you see up here: an eight-week wash-out period for oral products; a four-week wash-out period for transdermals; and a one-week wash-out period for vaginal products.

Screening mammography is recommended for all women aged 40 or older who participate in these trials; and, certainly, any finding suspicious of a malignancy should result in exclusion from trial participation and referral for further management.

Next slide, please.

Also with regard to inclusion criteria, when you look at the requirement for vasomotor symptoms at baseline, our inclusion criteria in this regard are based both upon the severity of those symptoms, as well as the frequency of those symptoms. And we require women, at enrollment, to be experiencing moderate to severe vasomotor symptoms. Gradations of severity are defined, as you see, on this slide, with "mild" being a sensation of health; "moderate," a sensation of heat with perspiration that does not stop activity; "severe," a sensation of heat with sweating that

does stop activity.

We also require women to have a minimum of seven to eight of these symptoms per day at baseline, or 50 to 60 per week.

With regard to the primary efficacy end-points for these types of trials, we expect o see a clinically and a statistically significant reduction in both the frequency and the severity of hot flushes, and we expect that reduction to occur within four weeks of initiating therapy, and it should be maintained throughout the entire duration of the trial, which must be a minimum of 12 weeks.

Subjective measures, such as patient diaries can also be used as primary end-points, and objective measures, like thermography, can also be used as either primary end-points or as supportive information.

Next slide, please.

With regard to safety monitoring--and some special considerations for these trials--the Division strongly recommends that endometrial biopsies be performed at entry to these studies and at study-end or discontinuation. Once again, follow-up mammography should also be performed in these patients, and all women with a uterus should receive 14 days of appropriate progestin therapy at the end of the clinical trial.

Next slide, please.

Okay--Section 2 of the document will focus on trials of combination estrogen/progestin products, or what we call "HRT trials," or "endometrial hyperplasia prevention trials."

Next slide, please.

Approval of drugs for this particular indication will mean that the combination drug policy applies, and that the lowest effective dose of both of the components must be determined in the clinical trials. The goal of these studies is to determine the lowest effective progestin dose for protection against endometrial hyperplasia or cancer. And trial design issues--a single trial, of 12 months' duration needs to be performed. There should be two treatment arms per estrogen dose. And this is a different suggestion than what you will find in the older version of your guidance document--and I'll talk about that in just a minute. We would also expect to see a dose-related difference between the two treatment arms.

In the past, we required three treatment arms for these trials. One of those treatment arms was to be an estrogen-alone arm. And because we know so much about the natural history of the development of endometrial hyperplasia following unopposed estrogen use, we did not feel that that was necessary, nor really was it ethical to continue to require that anymore. So now it's two treatment

arms per estrogen dose, and the two arms should have a different dose of progestin, but the same dose of estrogen.

With regard to inclusion criteria--again the Division defines menopausal status for these trials in the same way that it does for ERT trials. Wash-out periods from prior HRT use--again, the same for ERT trials, with the exception that if a woman is using a progestin-containing injectable or implant prior to enrollment, then a wash-out period appropriate to the product's half-life should also be followed.

Screening mammography--again, for all patients age 40 and over, and finding suspicion of malignancy should result in exclusion from participation.

Next slide, please.

Okay--with regard to primary efficacy end-point, in the earlier version of the document, when we required three treatment arms, the primary efficacy end-point for these trials was demonstration of a statistically significant difference in the rate of endometrial hyperplasia between the estrogen-alone arm and the estrogen-progestin arms, following one year of product use. But with the elimination of that estrogen-alone arm, we had to come up with a more appropriate primary efficacy end-point. And so what we chose here was a point estimate of hyperplasia risk, with the upper bound of a one-sided 95

percent confidence interval no more than 4 percent.

Next slide, please.

Safety monitoring in these trials--the Division requires endometrial biopsies be performed at baseline, annually, at the end of study or discontinuation; and trans-vaginal ultrasound can be used as a surrogate, but only if insufficient tissue is obtained on biopsy. Follow-up mammography is, again, recommended for women participating in these trials.

Other considerations that are covered in the older version of your document that will also be covered in the revised version include a request that sponsors assess the effects of these drug products on lipids and lipoprotein profiles, on carbohydrate metabolism, coagulation functions. We've also asked that they obtain some specific pharmacokinetic information, such as serum levels of drug and all metabolites.

Next slide, please.

Okay. I put this slide up here because, again, I think for clarification--let me talk to about why we're suggesting deletion of this particular indication from this document.

Drugs for this particular indication are not reviewed in the Division of Reproductive and Urologic Drug Products. They are reviewed in a separate division--that's

the Division of Metabolic and Endocrine Drug Products. There is a separate guidance document published by that particular division--it's dated April of 1994--that deals only with osteoporosis prevention. And so if you'd like specific information on design of those trials, you can contact this division and they will provide you with a copy of that guidance document.

But, very briefly, I just wanted to let you know that the requirements for a trial in that particular guidance document is for a single, 24-month, placebo-controlled, dose-ranging trial, with calcium supplementation.

Next slide, please.

Okay. That's the end of the older stuff. And what I wanted to do was end with a slide that lets you know that there are several other guidance documents that are in the process of being created, or are under revision. And I wanted to briefly let you know what those are.

The first is drug development guidance document for female sexual dysfunction--and I can tell you that this has personally occupied a great deal of my time over the last year. I think there's a tremendous amount of interest on the part of the public, as well as the sponsor community, in this particular indication. There is also a guidance document on--a labeling guidance document for combined oral

contraceptives, and there is a drug-development guidance document for vaginal contraceptive products that we are working on.

Next slide, please.

Okay. That's the end of my presentation. And--I'll stop here and allow you to ask me or Dr. Rarick any questions that you may have. And then we'll pose some to you as a Committee.

CHAIRMAN AZZIZ: Thank you very much, Dr. Allen.

Just to remind the Committee members, if you want to speak, just press the button. If it doesn't come red, then you go into a waiting line thing and your light turns green. Please identify yourself by name.

Dr. Allen, we have some questions for you.

Anybody have a question for Dr. Allen, for starters?

Well, let me go ahead and begin.

It's a lot of work that you put into this. This is a--it certainly does need to be updated. However, there's some issues that we don't need to discuss immediately, but I'd like to just make sure that we clarify them before we get into our panel discussion.

What was the rationale, again, for deleting "abnormal bleeding due to hormonal imbalance," from the indications?

DR. RARICK: Oh, I've got it. Sorry, Ricardo.

Did you want to answer that? Oh.

You'll notice that the third question posed to you for this afternoon involves a discussion of removing or discussing what could be done to support three of the indications. At the time of writing the drug development guidance document we were specifically concerned with the--quote--"abnormal uterine bleeding due to hormonal imbalance"--end quote--indication. So, for example, we actually haven't seen studies on abnormal bleeding due to hormonal imbalance that allowed that in the label. It's a very old label from 1976 or so that was put out through the Federal Register, that has remained on the estrogen products. Because of the vagary of its definition, unless this Committee can tell us that that's very clear, and that there are specific studies that we could ask for to be able to achieve that indication, we were thinking that it might be time to remove it. But we're open to all of your ideas about either leaving it alone, because it's existed for so long; how to do studies to support it; or what the potential impact of removing it might be if you feel there's a huge impact.

Does that answer that question?

CHAIRMAN AZZIZ: Another question on ERT trials--I'm sorry, VMS indication inclusion criteria: this

"FSH greater than 4, the estradiol less than 20"--I think that you might find some discussion today on that, just because the assays are so significantly different. And we will probably bring that up. I'm not sure that that's necessarily a question.

And then, "sweating," "perspiration," both the same thing--the same term. Yeah? Okay. I'm just--wanted to make sure that there wasn't something that we were missing on that.

And did you say that under VMS indication's primary efficacy end-points you were going to require objective measures?

DR. ALLEN: I said that basically, objective measures such as thermography can be used as primary end-points, or they can also be used as supportive information.

DR. FALK: I have a few questions.

It may seem like a minor question, but in the use of the endometrial biopsy, there are different techniques for doing an endometrial biopsy which vary significantly in their sensitivity. Could you take a more specific stance on what technique should be used?

DR. RARICK: No, we don't have a specific stand. We do give advice on making sure there's standardization of reading by the pathologists. But we don't necessarily make

a requirement for the type of pipelle, or novacurrette, or whatever. Usually a sponsor proposes the type they'd like to use, provides whatever information they have about the sensitivity and specificity of that.

If the Committee has a recommendation about needing a particular type of biopsy, that will be an interesting discussion.

DR. FALK: I have another, unrelated, question on the absolute contraindication for the use of estrogen in pregnancy. Broken record.

Specifically, on the endometrial cancer--the boxed warning on endometrial cancer, it says--the last line--"There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses --"--which is a reasonable statement. For pregnancy, however, there is no similar statement equating the data of natural estrogens, estradiol, estrone, estriol--comparing that risk with that of the synthetics--still be derivatives, namely diethyl stilbestrol. Is there any data that would warrant the absolute contradiction of the use of those natural estrogens in pregnancy?

And specifically I ask this--again, back to ART--is that there are certain aspects of ART, namely frozen embryo transfer or donor eggs, where we do support the

endometrium with estradiol.

DR. RARICK: Yes, that's very interesting. Of course, when writing this class labeling guidance for the post-menopausal indications, it's not in our usually thinking to try to think of all the possible off-label uses, but it's a good--it's a very good point.

And, no, I don't think that we have any data to throw in here about the natural versus unnatural or synthetic estrogens, although we do have a lot of data on many of the synthetic estrogens, where there aren't known adverse outcomes, in terms of, for example, hormonal contraceptives, are labeled specifically that they're not indicated in a pregnant woman, but that if used inadvertently, there's no specific birth defects or teratogenicity imposed by that use.

So if you--what you might be suggesting is--again, in the pregnancy section of this label, they're not indicated, but you're saying that they often are used off the label, and you would like a statement discussing: if used, blah, blah, instead of just the DES info?

DR. FALK: Yes, you--I mean, you've just made a very strong absolute statement here, and I think that statement should be softened for the use of the non-synthetic, natural estrogen.

DR. RARICK: Or even synthetic, I would--I mean,

you wanted to talk about non-synthetic, because that's what you're using off-label. But in terms of data--again, we were moving this from a boxed warning to a precaution, and so we didn't think about softening it up even further, but it's a good idea.

DR. FALK: I said "synthetic," meaning the--stilbene derivatives, but this--now, there may be different data on the ethinyl estradiol, as well, that's just not out. But, certainly, there's no data that's even conceivable--no pun intended--on the estradiol or estrone.

CHAIRMAN AZZIZ: Any further comments or questions simply for Dr. Allen regarding this. We'll certainly get into the Committee discussion in a minute, but--okay.

I'd like to not have a break. We've just had lunch and we have a lot of work to do, so we'll just take individual breaks, I guess.

Let's go ahead and go to the open public hearing. We have a total of what looks like seven presentations, but actually five letters. We're only going to read one of those letters. They're all similar, and so we're just going to go ahead and read one letter. Are you going to mention all the different--

MS. PETERSON: Yes, I can do that.

Actually, we--all the letters--I have four letters, and they all contain a common theme, and that theme

being the concern with the removal of the osteoporosis discussion from the patient package insert.

So--anyway, we've decided just to read one. And actually we've heard from the National Osteoporosis Foundation, from Dr. Charles Hammond, a private practitioner at Duke University Medical Center, and from Dr. William Andrews--again, a private physician in practice; past president of the American College of Obstetricians and Gynecologists.

And what I'm going to read is the statement from the American Society for Reproductive Medicine.

"It has come to our attention that the Advisory Committee for Reproductive Health Drugs will be discussing a draft of a new labeling guidance for on-contraceptive estrogen drugs at its next meeting. The American Society for Reproductive Medicine, whose membership includes more than 9,000 professionals dedicated to reproductive health has some concerns with the draft guidance as it has been presented. Specifically, the new guidance deletes all mention of osteoporosis from the information for the patient section. The deletion of this text removes important information regarding of the use of non-contraceptive estrogen. For years clinicians have utilized the information on the importance of estrogens on bone to counsel their patients on the prevention and treatment of

osteoporosis. This opportunity may be compromised if the suggested changes to the labeling guidelines are approved. We find it particularly confusing that the indication remains in the information for physicians section. Describing the benefits and potential side effects of any medication are an important part of counseling patients. Having one set of benefits described to them by their physician, and a different set in the literature that accompanies the drug will have a deleterious impact on the doctor-patient relationship."

"The use of estrogen replacement therapy has become an important part of the practice of many of our members. We urge you to retain the information regarding the prevention and treatment of osteoporosis in the patient labeling in your guidance."

"Thank you for your consideration of our views, and we look forward to working with you.

CHAIRMAN AZZIZ: Thank you, Jayne.

We have three speakers today. Please--I ask you again to limit yourself to five minutes so that everybody can have an opportunity of speaking.

We have Amy Allina of the National Women's Health Network.

MS. ALLINA: Is it on now? Yes. Okay.

My name is Amy Allina. I'm the Program and Policy

Director at the National Women's Health Network.

As most of the Committee members know, the Network is a non-profit, science-based consumer advocacy organization. We don't accept financial support from pharmaceutical or medical device companies. We're supported by a national membership of 12,000 individuals and 300 organizations.

In January of this year the Network submitted comments to the FDA staff on its proposed changes to the labeling guidance for non-contraceptive estrogen drug products, and after the reviewing the newest revision of the draft guidance, we didn't see most of our comments reflected, so we thought we would come today and put them out for the Committee members. And if you find that you agree with any of our comments, we hope you'll raise them in your discussion and advise the Agency on addressing them.

As we did in our January comments, I'd like to begin by expressing our support for some of the additions to the labeling guidance. In particular, we're pleased to see the new language i the warning section about venous thromboembolism. There are a few changes that we're concerned about--or changes that weren't made that we'd like to see made.

In both the physician and the patient labeling of the draft guidance, the language addressing the risk of

breast cancer associated with estrogen replacement therapy doesn't adequately or accurately describe the most recent data available. A 1997 summary of every study of estrogen replacement therapy and breast cancer published in The Lancet found that using ERT for five or more years increased a woman's risk of breast cancer by about 35 percent. This finding was based on the experience of over 52,000 women in 21 countries. The Network believes that both the physician and the patient labeling should reflect this data.

We recognize that there are conflicting studies, and that the question won't be completely settled until the results of a long-term randomized trial are in, but in the meantime we believe that it's important to share what it known. We've provided the staff with some recommended language which we would be happy to share with Committee members if that would be helpful.

We also recommend that the labeling should be revised to add a warning to physicians and patients that mammography has been found to be less effective as a screening tool in women who are taking estrogen therapy. Because it increases breast density it makes mammograms harder to read, leading to less reliable results. The patient labeling should include this information, and it should caution women taking estrogen that they should be especially attentive to any changes in their breasts,

particularly changes that take place in only one breast.

There are a number of studies which support this position, and I have them listed in my written statement, but I won't go over them right now.

We share the concerns expressed in the letter that was written about the need for information about osteoporosis in the patient labeling, but I understand from Dr. Allen's statement that will be taken care of.

The draft guidance also doesn't have language which has been on the label about when estrogens are ineffective. This section explains that there is not evidence that estrogen is effective for treating depression or for keeping skin soft. And we recommend keeping the language on the patient label. We recognize there are small and inconclusive studies on estrogen's effect on mood and skin, but we don't think their results are sufficient to warrant omission of the warning. And we also recommend that Alzheimer's disease should be mentioned in this section, since it's another unproven claim that's made for estrogens. Those of you on the Committee who are clinicians know that women often have misconceptions about estrogen's ability to affect these conditions, and we're asking you to address those--help address those misconceptions by including information in the label for patients.

Finally, we recommend retaining some language

about uterine fibroids in the precautions section of the physician label. Fibroids are common in women, especially as they approach the age of menopause, and it's important for doctors to know that hormone therapy may increase fibroid size.

Thank you for the opportunity to share the Network's comments on the draft, and if you have any questions I would be happy to try to answer them.

CHAIRMAN AZZIZ: Thank you very much

Dr. Robert Lindsay--if he's in the audience.

[No audible response.]

Next speaker is Dr. Margaret Weber. Is she in the audience? Assistant Vice President, Global Medical Affairs, and Associate U.S. Medical Director for Wyeth-Ayerst Pharmaceuticals.

DR. WEBER: Good afternoon.

I'm Dr. Margaret Weber, and I'm here on behalf of Wyeth-Ayerst Pharmaceuticals. Wyeth-Ayerst is a leading pharmaceutical company with a major research facility--the Women's Health Research Institute--which is devoted exclusively to women's health. Accordingly, our comments today are focused on two issues: first, post-menopausal osteoporosis, a significant public health issues; and, second, the importance of retaining additional information about this disease in the labeling guidance for

non-contraceptive estrogens. Originally I was also going to address a third issue, which was the patient indication for osteoporosis, but Dr. Allen made it clear that that was inadvertent. So you just saved me ten pages of my speech [laughs.]

Let me just start with the first of a few facts that demonstrate the public health impact of post-menopausal osteoporosis. Today women can expect to live another 30 years after the menopause. Estrogen loss at menopause can lead to rapid and significant bone loss. In fact, a woman can lose up to 20 percent of her bone mass in the first five to seven years of menopause. Given the millions of baby-boomers entering the mid-life, the prevention of post-menopausal osteoporosis, and its associated fractures, is extremely important in reducing health care costs and elder disability.

Given the public health consequences of osteoporosis, physicians must be able to adequately counsel their patients, the benefits of estrogens, particular for the prevention and management of post-menopausal osteoporosis. Wyeth believes that the current estrogen labeling provides information that is very relevant to the use of estrogens for this disease. Therefore, it is important to note that the FDA draft guidance to be discussed here today has deleted a section that we believe

is critical to estrogen labeling. Recognizing that the labeling can be an important counseling tool, for providers and patients, we would like to bring this section to the attention of this committee.

In the current physician labeling, the indications section contains information about risk factors for osteoporosis, such as race, family history, small body build, cigarette smoking, lack of exercise, and nutrition. It also discusses other factors that are relevant to the prevention of osteoporosis, such as weight-bearing exercise and adequate calcium intake. And, finally, it also presents a summary of epidemiological data--and I quote--"Case controlled studies have shown an approximately 60 percent reduction in hip and wrist fractures in women whose estrogen replacement was begun within a few years after menopause."

The 1999 draft guidance has deleted this important information about the risks and management of osteoporosis, but this section is critical to the prescribing of non-contraceptive estrogens, and that's because it gives health care providers accurate and relevant information about post-menopausal osteoporosis. This is information that they can use when counseling their patients. Therefore, this information--this section--should remain in the labeling.

Thank you for the opportunity to bring this to

your attention.

CHAIRMAN AZZIZ: Thank you very much.

Anybody else in the public would like to comment on this?

[No audible response.]

CHAIRMAN AZZIZ: If not, let us proceed with Committee discussion. In questions--I will read each of the questions individually and proceed down.

Before I do, does any of the Committee members have any general comments or questions for staff, before we undertake this?

[No audible response.]

CHAIRMAN AZZIZ: Very well. The first question is: does the Committee recommend study of hormone replacement therapy--HRT--in menopausal women with less than moderate to severe, or less frequent than seven to eight per day, or 60 per week, vasomotor symptoms.

So this is in regards to the definition of vasomotor symptoms.

DR. HAMMOND: I guess I have a question. Are we saying--is this a new indication? Is that what we're asking, as a new indication?

DR. RARICK: Oh--sorry.

Current labeling describes that it's approved, and the indication is obtained is moderate to severe vasomotor

symptoms, and we've defined them as described.

We have much interest, from both industry and consumers, of what to say about less than this, and is there room for either broadening this particular indication, or a separate indication for less moderate to severe, or less per day.

Currently, sponsors are required to find women that actually do have--have to wash out from previous therapy, have at least 60 moderate to severe vasomotor symptoms per week. And there is--we need your discussion about whether there's room for the indication in less moderate to sever, and if there is, is the one clinical trial appropriate? Is there--do you have any comments on the clinically significant differences between groups that you'd like to see.

One of the reasons we have it written this way is because we're very familiar with this data. We're very familiar with the kinds of effectiveness end-points we look out when people start with the baseline in here.

If we are to broaden our indication, we need your comment as to--if somebody has five a week, then what is the clinical relevance of therapy? Does it have to be zero, etcetera, etcetera.

Just want to hear your thoughts--or do you want to stick with the original 1972 version of estrogen labeling,

which said this is what we know it works for, if given in the right dose.

DR. LERNER: I can only speak clinically anecdotally, but that seems particularly stringent to me, and maybe it's just my sort of liberal, professional New York clientele but I, you know, don't know that people are going to tolerate that as a definition.

DR. HAMMOND: Well, having done objective testing, if you don't have that many--oh, Dr. Hammond--if you don't have that type of objective testing, then it's very hard--that frequency of hot flashes, you can't pick them up in a study. Because if you monitor a patient for six hours, which is normally what you do, if she doesn't have that many hot flashes, you won't see a difference with the treatment. Because if they're only having a hot flash every hour--they usually have them about every 90 minutes when it's severe. But if they're not have the severe hot flash pattern, and you might monitor them for six hours and not pick a single hot flash at baseline, so therefore you couldn't demonstrate an effective medication. You could only do this with a diary.

CHAIRMAN AZZIZ: My comment--I mean, this is, again, about this definition. It's purely a definition here. And the question is, should sponsors be required to find these women, wash them out, not treat them, and then

treat them?

And my impression--and, again, we'd like to get the Committee's--my impression is that, yes, it is stringent. This is not what is clinically useful to us, but on the other hand, because of the significant placebo effect of these medications, there's a 50 percent reduction in vasomotor flushing with placebo alone. So that I think you do need to have fairly clear-cut affected women for these type of studies. I don't think you can get around that very well.

But anybody, again, disagree with this? I mean, this is the recommendation. Any disagreement from the Committee? Does the Committee feel that perhaps these are overly stringent and we should, for clinical trials, recommend lesser stringent criteria?

DR. RARICK: I'm sorry, I have the mike now. I'm not on the Committee.

But just for your further discussion, one question is--okay, we would agree that the easiest way to show effectiveness of your estrogen product is to find these more severe women, have a placebo-controlled trial; you have to deal with the 40 to 50 percent placebo effect, and you can still show a difference.

Our question is: if a sponsor came to us and said, "Well, we really want to do something less severe or less

often," and as long as the onus is on the sponsor to find a clinically relevant difference between their placebo group and their drug-treated group, does this Committee think that is a reasonable design that would change the indication for that product?

DR. FALK: I would think that this is overly stringent, considering the fact that the criteria used is not the most objective. So that I think if you--if one wanted to be more--if one wanted to maintain stringency in objective signs or symptoms--or signs, really--then I would go more by the laboratory data and allow more leeway in the clinical--in the subjective data.

DR. HAMMOND: Well, I guess I would have a question--are we really talking about, perhaps, a new indication around the peri-menopause. I'm wondering--yes. Because it seems to me there are only two groups of people that have these mild hot flashes. They're either women who are in the peri-menopause, or they're women who are well past the climacteric period. And so I'm wondering if that's what we're talking about.

DR. RARICK: Certainly, you notice we left that word out of any of these questions, but thank you for bringing it up.

That's something for the Committee also to let us know. We, as a division, have tried to manage the question

of the less than menopausal women as simply that, but simply still having the same symptoms that a menopausal woman might experience.

If you feel that peri-menopause itself is a specific indication, we need to hear that discussion. We had crafted the questions--and I think the last, or the next to the last, is specifically your question: what if someone doesn't meet the criteria for menopause? Is that a different indication? Or, if they're not meeting the criteria for menopause but they have vasomotor symptoms, are we simply saying vasomotor symptoms--whether they're post-menopausal or peri-menopausal, or what. I don't know.

But that is--the intent of the question is: do we broaden vasomotor symptoms? Do we make "mild" a different indication? Do we make peri-menopause a different indication? And, if so, there's a lot of clinical design impacts that that would have.

CHAIRMAN AZZIZ: Yes, I think we'll talk about peri-menopause in a minute, because I think it's a bigger subject.

But according to this question, anybody have further comment? I mean, it sounds like if the burden of proof is going to be on the sponsor, then certainly there are clinically affected women who have less hot flushes who are in need of care. I mean, you're right. I think that if

we're stringent, that simply will favor an observed difference, but if you have enough patients, perhaps you will be able to observe a difference.

I think I would probably feel freer relaxing it, in spite of my earlier comments.

Anybody else's thoughts?

DR. LERNER: I agree.

DR. RARICK: Does the Committee believe that if something was approved for moderate to sever that it would automatically treat mild?

CHAIRMAN AZZIZ: Probably yes.

DR. RARICK: So, for example, to expand the indication, for a company that comes in without choosing women with this severe, and so gets just vasomotor symptoms--a sponsor who had had to do the more severe would automatically get the mild?

CHAIRMAN AZZIZ: I would think so. I mean, the reverse is certainly not true. I mean, there's a number of drugs that can treat mild symptoms in women, but that certainly are not effective in the truly menopausal woman. But I think the reverse is probably true. If they treat effectively women in full-blown menopause with this kind of symptomatology, I don't see--I don't think any of us would have any wonder about milder symptoms, for sure.

Perhaps it is now time to bring up the

peri-menopause. Certainly, we've touched and danced around that subject for a long time. The FDA has no real--that I'm aware of--no drug that has targeted peri-menopause and, in fact, it doesn't exist, really, in this realm unless we think so.

So I think it is truly one of the most severely under-treated, under-recognized disorders of women today. And having said that, though, I'd like to have other Committee's comments on whether drugs should be formulated for the treatment of peri-menopausal women.

DR. LERNER: Jodi Lerner.

I assume that the old indication would be abnormal uterine bleeding, sort of, that doesn't need strict criteria for menopause, probably tries to encompass some of the anabulatory peri-menopausal women in that realm, and I assume that that's sort of what it's trying to fit in.

So I think even by eliminating that one indication, you may then lose whatever sort of small peri-menopausal inclusion you would have had, per se.

CHAIRMAN AZZIZ: But if you're getting the gist of the--the recommendations--I mean, certainly, as I said before, if they have approval with severely affected patients, that probably would allow patients who are less affected to be--but if somebody wants to study lesser affected patients to have a lesser affected peri-menopausal

indication, I think that that would also be viewed favorably by the Committee. I think we would like to see that.

DR. RARICK: Maybe you could just go to question 4, then? And--I think that's what you're answering: is that you think there is a population that requires therapy, called peri-menopause.

I would like the Committee to comment on trial design, so that, for example, would you be suggesting that the doses would be different for these symptoms in the peri-menopause? And would they change over time as women became menopausal? If you're doing a three-month study, are you then damning yourself, because you're no longer peri-menopausal at the end of the three months, etcetera? Help us with these questions.

DR. FALK: Richard Falk.

The problem--the reason we're wrestling with these problems is we have--we're dealing with some archaic terminology here. And we're trying to answer archaic terminology with modern, up-to-date terminology.

So, for instance, we're talking about a variety of hypo-estrogenic states--or a continuum of--progressive to a point of hypoestrogenism, and we use the word "hormone" or "estrogen replacement therapy." The implication of "replacement therapy" is that you replace what's deficient. And so, theoretically, at least, in an ideal model, you

would use less estrogen for a person who's less deficient, more estrogen for a person who's more deficient. In practice purposes--in the practical sense, it doesn't always work out that way because we are treating the often subjective symptoms of hypoestrogenism that may or may not be related directly to hypoestrogenism. And that's why we see the high placebo success rate with some of these things. Yes, a woman is hypo-estrogenic, yes, she has hot flushes--true, true, and maybe related.

So that I think--if it's at all possible--I'm not foolish enough to say let's do away with that terminology of menopause and peri-menopause, but I do think--well, I do think we ought to talk about physiologic hypoestrogenism and its symptoms, and then that makes it a little easier to address this.

So it doesn't make any difference if you're having a few hot flushes or a lot of hot flushes. If you're symptomatic, and you're hypo-estrogenic, then you would be a candidate for this--you could be categorized as--in this grouping.

CHAIRMAN AZZIZ: I think that in regards to the trial--number 4 obviously deals with both the definition and trial, and you've just suggested trials. There's a real problem, and that is that to diagnose menopause, according to this criteria, and--which is a true criteria--you depend

on an assay for FSH, and you depend on an assay for estradiol. And if you were to say you want to diagnose peri-menopausal women--which obviously is what we need to do--then we'd have to change the FSH or estradiol criteria.

The real problem is--those of us who run endocrine labs--the estrogen--estradiol--assay is lousy. It is a worthless device--no, actually, it's--it belongs to somebody else--but it's a worthless kit in the vast majority of the cases. It doesn't measure what you want it to measure.

So asking for estradiol levels of less than 20 picograms per ml is foolhardy because, in fact, most menopausal women will have assays that will run anywhere between 50 and below 50 picograms per ml and below. So I don't think estradiol should be used as part of this criteria. I mean, certainly, Richard will--you may, agree or not. I mean, certainly better assays are already--from the maturation index; things of this more primitive nature.

FSH levels--I don't think today we're using the old cutoff of 40 mIU per ml. I mean, 35, or even 30 is considered menopausal in most cites. And certainly, you can put--you can select a group of peri-menopausal women whose FSH levels fluctuate between 20 and 30, and then you get into the 30 and above, and that becomes, sort of, true menopause. But, as Richard said, it is a continuum. So we're grappling with it.

The FSH assay will be much more accurate than the estradiol assay, though--in general.

DR. FALK: I totally agree with that. In fact, I would almost substitute for the estradiol, LH, and do an FSH And LH assay, which would probably give you a better index of the ovarian function than an estradiol. I don't know that the assay is lousy. It may be a fluctuate--too fluctuating a system to pick it up with one spot level.

DR. DATTEL: This is --Bonnie Dattel.

This is a little out of my bailiwick, but as an objective observer, it seems to me that you're kind of limiting yourself with the definitions, and then you have to include something separate from the peri-menopause. And if you were more global in your definition of the patient population, it would include this whole spectrum of women, without really locking yourself into this definition--just as an objective--

CHAIRMAN AZZIZ: I'm sorry, could you clarify that again? I missed.

DR. RARICK: Well, let me see if I've captured it.

I think what Dr. Dattel is suggesting is that we get away from the "archaic"--as Dr. Falk would call it--and not give names to these things, or try to define them with any particular FSH or LH level. But, then again, I want to hear the Committee's comments--then can we simply use

symptoms, and not necessarily require a label of "peri-menopause" or "menopause?"

And, then again, if you're going to that, tell us what we should do about contraception and the peri-menopause.

DR. HAMMOND: Mary Hammond.

Going along with that, I think you're right about the FSH. I think most of us use that in our practice. And if there's a borderline elevation or a significant elevation in FSH and people are symptomatic.

But, again, so many of the symptoms that our patients have in the peri-menopause are not as simple as your indications. I mean, there's not necessarily vulvar atrophy, and there's not severe hot flashes. There's this general feeling of malaise. And so I'm concerned about both the diagnosis and the end-point that you would use for that indication.

DR. FALK: I don't think--I agree exactly with Mary, but I don't think you can go just by symptoms. I think that would be a major mistake. But I think with the laboratory back-up, with the criteria--and, again, I would call this "functional" or--"functional hypoestrogenism," or "gonadal hypo-function,"--

[Laughter.]

DR. FALK: --without--with symptomatology. And so

I think you have to use both of them--much like you--polycystic ovary would be anovulation, with or without hirsutism.

CHAIRMAN AZZIZ: You know, Richard has forgotten what he's taught me--but it's "hypergonadotropic hypogonadism" is really what we're talking about here--huh--and that's truly what it is. We have--and that's why this whole menopause--this is the same thing as the younger individual whose ovarian--you know, who's castrated or so on--simply hypo--but we can't use that word in patient labeling and you can't word in practitioner.

So, unfortunately, I think we're going to be stuck with these "peri-menopause," "menopause" terms. But I think in there we should clearly indicate that estrogens are indicated for the treatment of symptomatic hypergonadotropic hypogonadism. And that's truly what we're treating.

In regards to the remark on LH, I do think that the LH assay will simply confirm that it is a generalized excess of gonadotropins. There are cases where you can have an isolated FSH elevation--you know, you get them at the mid-cycle or something of that nature. But, in general, if you get LH and FSH that are elevated--not used clinically, but for trials--then that would be more confirmatory of menopause than, say, estradiol levels and so on.

DR. RARICK: I was going to ask you both to

comment, because Dr. Falk's been commenting on hypoestrogenism, but doesn't want us to use estrogen levels--suggesting an LH level as a cutoff. Did you give us a number--a definition?

DR. FALK: No, I can't right now give you an absolute number. The problem with all of these assays--LH--is that you have pulsatile levels, and so I think that--you know, we now that there may be higher levels in a large population, but in an individual it might not be significant. So--for instance, if you got it just pre-ovulatory, you can have a very high LH level that would not indicate ovarian failure.

But I just think--my point was to use multiple tests to confirm, along with the symptoms. And I think if you have a woman who complains of hot flushes, and is amenorrheic, and she has an elevated FSH, and she has an elevated LH, then I think it's safe to put your money on a diagnosis of ovarian failure.

DR. HARRIS: I just had a quick question--and maybe I missed it because of jet lag.

The implication of the question is that without a clinical trial, this would be an off-label use of the--of estrogen?

DR. RARICK: Currently, the labeled indication is "moderate to severe vasomotor symptoms associated with the

menopause." Depending on how deeply you look into that definition--yes, anything else would be off-label use.

Let me get back, also, to Dr. Hammond's comment--and the Committee might want to elaborate--is the peri-menopause--are you thinking health-related quality of life sort of claims? Or are you thinking of different claims outside of the usual estrogen claims?

DR. HAMMOND: I wasn't so much asking you for that as an indication, but explaining that, for most patients that present, it is a quality of life issue that they present with, rather than the more specific.

CHAIRMAN AZZIZ: You know, in regard to the peri-menopause, I don't think that you necessarily need to go to other indications. I mean, clearly, if a sponsor wants to get an indication for improvement of quality of life, or improvement in Alzheimer's, or whatever it is, they will need a separate targeted trial.

But, certainly, from a point of view of general recommendations, estrogens are going to be useful for this hypergonadotropic hypogonadism, whether we want to call it the "transition of peri-menopause," or "in-menopause," or "menopausal," or whatever term we want--and the problem is those are all wrong terms. That's the real--I think as Richard had said. So, I do think so.

But, in regards to trial design, we've talked

about patient selection. I think you probably need to say generally FSH levels of over 30 or 35--generally--because, you see, the sponsors of trials really should be able to present their own controls. It's no different than any other laboratory that's doing this. They should say, "In our lab, menopausal women, according to our survey of 100 menopausal women--"--or whatever it is--"--this is the level." I mean, it happens with estrogen, it happens with testosterone.

So I don't think that it would be healthy for the Division to state a single, absolute level, because then you're going to be forcing a lot of significant problems from a laboratory point of view.

As far as design, I don't think--I mean, I don't have any other significant recommendation, other than saying they should follow the general designs. My question to you is, though: if the Division feels that peri-menopause is now part of this menopausal status, and drugs that were proven effective in menopause may be proven now effective in peri-menopause, is that going to be an automatic thing? I don't think it's a terrible thing, but I think--this is my question to you now, from an administrative point of view.

Are drugs that are now approved for menopause--improvement of vasomotor symptoms in menopause--would they then be automatically listed--have a

listed indication of peri-menopause?

DR. RARICK: Most likely not. A study would need to be done to show that the types of vasomotor symptoms, for example, that are in the less than menopausal status woman are treated appropriately at the least--the lowest does that's effective. So, for example, maybe it takes more estrogens in the peri-menopause, maybe it takes less. I don't know.

And also if the symptoms are different than our usual criteria of seven to eight per day, we would want to see that a drug did better than placebo in a woman who is less effected.

So I think--what I'm hearing is you don't ind the idea of the fact that--I mean, women are--we all know women are being treated with less than seven to eight per day vasomotor symptoms a day, but why can't the company go ahead and do a study and show us that they are effective in that population.

That's kind of what I'm hearing--and that you'd like us to be more general in our definitions and allow some room.

DR. TRUSSELL: Why would a company want to do that? They can already sell their product to the same group without having to undergo the expense?

CHAIRMAN AZZIZ: Well, I mean, we all know acne is

treated by birth control pills, but a company who doesn't need to be called, that a small study with birth control pills and acne, and is now using it as a major marketing tool, and they're dominating the market because of that. There's a lot of women with peri-menopause. And if you get something that you can actually market on tabloids--that's going to be much more effective.

So I think that that's really going to be their concern. But, certainly, we would like for them to market things that are indicated. I'm not sure about "like" as the right word, but--

DR. LERNER: I think the hardest thing, then, would be the definition--and maybe we're digressing a little bit, but we're already having a tough enough time finding a true definition, or strict definition for menopause. I think once you open it up to peri-menopause, it's--you have 900 different variables, of varying length of time, various laboratory assays. I don't know that you can ever standardize that in any reasonable way.

CHAIRMAN AZZIZ: Just a--to move the conversation--to move our discussion on--anybody else have comments on number 4--question number 4?

Again to summarize--I think, Lisa, you summarized it well. We don't feel so comfortable with a very strict definition of menopause, at least the way it's stated. We

certainly do think that peri-menopause should be included and is a group that is worthy of study. And, again, there are ways to diagnose these women, by either lesser FSH levels, lesser symptomatology.

Any other comments to number 4?

DR. RARICK: Can I ask one follow-up question? I'm sorry, it's not one of the questions, but since the discussion is leading this way--does the Committee have any comments about treating the peri-menopausal woman with combined oral contraceptives, or oral contraceptives for contraceptive use, and also treating their vasomotor symptoms, versus trials where you're treating vasomotor symptoms, but not giving contraceptive coverage.

Is there any considerations there about the hormones used?

I don't know if you heard that question, Ricardo.

The question is: peri-menopausal women are--could potentially still be in need of contraception. Is there a need for contraceptive hormones to be studied in vasomotor symptoms in the peri-menopause?

DR. FALK: I think from a practical point of view that's done an awful lot now, for several reasons. Number one, that population of people may well need contraception; b) that population also is more desirous of having a monthly menstrual flow than, perhaps, an older population is.

So, all in all, they feel more--quote-unquote--"normal" on a combination type of medication which does give them all of those advantages.

CHAIRMAN AZZIZ: I mean, I just came back from ACOG, discussing various guidelines. And certainly the feeling is that for the older peri-menopausal, the mature woman, oral contraceptives, in the absence of--if I can't say "mature women" are in the audience--is--oral contraceptives are actually the primary mode of therapy, rather than estrogen or hormonal replacement. So, in fact, the answer is yes.

But I was under the impression--correct me if I'm wrong--that studies have already been done with the use of so-called "low dose" oral contraceptives in peri-menopausal women, or at least in older women.

Am I wrong?

DR. RARICK: Well, certainly, the contraceptive effect is believed to exist for a woman who's over 40, but the actual trials are done, usually, up to about age 40. But there's no reason to believe the contraceptive effect goes away.

My question for this committee is: is a trial design in peri-menopausal women--is it more appropriate to look at ERT for vasomotor symptoms, or contraceptive hormone levels for vasomotor symptoms.

CHAIRMAN AZZIZ: Certainly I would look at--I don't know if it's more appropriate, either one. I mean, I think the populations are different. The peri-menopausal woman would tend to ovulate occasionally, and sort of mess things up with the HRT. So, in general, it's better to use low-dose oral contraceptives. But many of them are not candidates for it. I mean they have medical disorders by that age that preclude that.

So, I think--I mean, both require study, because the populations are used--and the off-label use is currently tremendous. So, in a sense, you're not going to stem the barrier--the tide, you're simply going to provide information, obviously.

Any other comments on this question?

Before we continue, I've been told that Dr. Robert Lindsay, one of our speakers, just arrived. He's had airplane delays.

Let's go ahead and open that--open the public hearing so we can hear his comments.

Dr. Lindsay, you have five minutes, as you're aware. Thank you.

DR. LINDSAY: Thank you very much, Mr. Chairman. My name is Bob Lindsay, from New York--Columbia University. And I'm professor of medicine, and Past President of the National Osteoporosis Foundation.

I appreciate the chance just to address a couple of issues related to estrogen's effects in post-menopausal women, and particularly its effects on osteoporosis.

One of the issues that has come up fairly recently has been the suggestion that in studies not designed to evaluate, as a prime outcome, the effects of estrogen on osteoporosis has been the finding that fractures were equal number in placebo group and the estrogen group. Pre-referral clinical fractures are very difficult to find as an end-point for a variety of reasons. Firstly, they're not particularly common. And, secondarily, even in studies designed specifically to look at that outcome, the effect is comparatively modest. These data are from the well-known Merck studies looking at aldendronate, demonstrating the very modest effect of aldendronate on peripheral fractures in the so-called two study--a study of some 4,000 individuals followed over a four-year period. The note a modest effect, and a very borderline statistical significance of that effect, when one looks at peripheral fractures.

Now, the effects of estrogen are well known. We've known for a very long time--in fact, since Fuller Albright in the 1940s--that estrogens actually reduce bone turnover, prevent bone loss, and consequently are as--bone active agents for as long as they are given. And these are

all data from our group, demonstrating the prolonged effects of estrogen in post-menopausal women.

Now, those data have--it has been argued, do not related--because they measure peripheral bone, don't relate to bone at important sites of fracture, namely the spine and the hip. But those data also showed positive effects on estrogen at the spine--that is often forgotten--and also the same effects at the hip, albeit in a cross-sectional manner, because the techniques for those measurements were not available when the study was originally designed.

However, the findings in the spine and the hip, and those data, are identical to the findings in the PEPI studies, and--which are perhaps the best known of the studies in looking at the effects of estrogen and HRT on spine and hip--and are comparable to all of the other prospective controlled clinical trials in which bone density has been looked at as an outcome.

Now, it's often argued from that, that we have bone density data, but we have comparatively little clinical trial data for estrogen's effect on fractures. However, when one looks at the clinical trial data for fractures, there are, in fact, two clinical trials that have looked at fractures prospectively: our own data that looked at 10 years' worth of data and demonstrated a reduction of vertebral fractures; and the Lufkin data, which are shown on

this slide--which, if I were closer to the screen, I could probably read which one it is--demonstrated a significant reduction in only one-year therapy with estrogen.

Now, I've been a little naughty in this slide, and I admit to that, because on this slide I've demonstrated the effects of a variety of agents on vertebral fractures on the top, and on bone density on the bottom. And I want to point out that despite the diversity of effects of bone density, there is a remarkably similar outcome in terms of vertebral fracture. And for those agents on which we have data on femoral neck fractures, the same is evident--that bone density changes that occur account for only some 25 percent of the reduction in vertebral fractures that one sees.

Consequently, the idea that one would not have, in estrogen labeling, effects on osteoporosis, which affects, as you know, this huge number of post-menopausal women in particular, and would not be able--that they would not be able to learn the benefits of the prevention of bone loss, and the reduction in bone turnover, and presumed fracture outcome from that, I believe would be detrimental for the health of the post-menopausal women.

I, once again, would like to thank Mr. Chairman and the Committee for their indulgence, and the chance to present those data. Thank you.

CHAIRMAN AZZIZ: Thank you very much. We will be

discussing that whole issue in a second.

Let us continue with our questions.

Number 2: Please provide comment and recommendation concerning endometrial safety monitoring in vasomotor studies--vasomotor symptom studies; and baseline and end-of-study endometrial biopsies needed in three-month ERT trials?

DR. DATTEL: Well, I have an opinion as a woman. I think that's ridiculous. Three months is really--I mean, correct me if I'm wrong--three months is a rather short period of time to require a woman to undergo two endometrial biopsies, and it probably doesn't provide the information that you're looking for in a three-month period.

DR. LERNER: I concur. I can't imagine that you'll find any sort of change.

DR. FALK: But I do think that endometrial safety monitoring could include ultrasound, which is certainly not very painful, and would at least give you an idea if something should be followed up on.

DR. HARRIS: I guess the real question is what is a reasonable time, based on the natural history of unopposed estrogen exposure on the endometrium. And though the statement suggests that endometrial cancer is the lesion, is that data well supported? Is it endometrial cancer, or is it atypical adenominous hyperplasia in unopposed estrogen?

CHAIRMAN AZZIZ: I think the--there's two questions here, and that is really whether you need to do beginning and end studies of endometrial biopsies, and whether that should be applied to a three-month study, I mean. So the questions are different.

Clearly, I think all of us would agree that if it's a three-month trial, the beginning and an end is totally unnecessary, painful, and it's just not valuable, because we know that in three months you're not going to develop either endometrial atypical hyperplasia or cancer or anything else. A baseline I think is always valuable in any study, just for the--obviously, from a--the sponsor should do that from a legal point of view, just so that they don't develop--they discover that cancer, but we should do it from a health point of view.

But the question is--then the second question is, if we have a 12-month study, should we do an endometrial biopsy. We need to give some sense of recommendation to the FDA as to when we think an end-of-study biopsy should be done. I mean, recently we had a product approved for the treatment of osteoporosis who had absolutely no systematic view of before and after and, of course, only in a small trial. So that was the opposite problem. So that was also a problem.

So at some point we need to give the FDA some

sense of when that needs to be done. I certainly think three months is unnecessary if they only do it for three months. I would say certainly, if it is 12 or more months, they should have an endometrial biopsy at the end of the study.

But I don't know about six to 12 months--I mean, what--three to 12 months? I have no clue. I think we'll hear from other--

DR. FALK: I think that it's only prudent to follow the endometrium by at least sonography. And as far as the three-month versus 12-month, if I'm not mistaken--I'm trying to think of the original studies on endometrial cancer--they were every use estrogen, is that not correct?

DR. RARICK: You're absolutely correct. For cancer, these are epidemiologic results that show that unopposed estrogen is related to an increased risk of endometrial cancer. In a one-year trial you can certainly, though, elicit lots of endometrial hyperplasia, which is why we've designed the hyperplasia-prevention trials at the one-year mark--and sometimes they're done for longer. But, again, anything that's a year or longer, we already have designs in place, or recommendations in place, for biopsies.

And, again we are not advocating estrogen-alone for a one-year period in a woman with a uterus at this point.

DR. LERNER: Well, then why are the safety trials only for three months, then?

DR. RARICK: This is not a safety trial; these are vasomotor symptom studies. We think that--the usual end-points we've used in vasomotor symptom studies has been that a three-month trial is adequate. And, in fact, those labels read to use them for three to six months for vasomotor symptoms only. We don't have trials for vasomotor symptoms that go on.

CHAIRMAN AZZIZ: Just for the information of the panel--I mean we're looking at different indications. If somebody wants to come for an indication of vasomotor symptoms, it's only three months that they're required to. In that case, endometrial biopsy at the end is superfluous. If they want to do osteoporosis, then we're talking about trials that are 12, 24 months.

Are there any trials--are there any indications for which a treatment of three to 12 months would be sufficient. Because if there is, then we need to discuss it. If there's not, then we just need to sort of move on.

DR. RARICK: If a sponsor proposed something in between, we would have to work with them individually, in a case-by-case sort of scenario.

Just to add to the picture--I hear Dr. Falk mentioning looking at the endometrium at some level in a

three-month study. If everybody receives a progestin-challenge test at the end, do they still need to have endometrial monitoring?

DR. FALK: I think for a study subject, the answer is yes. I don't know that progestational challenge test would wipe out the endometrium--atypical endometrium completely.

DR. DATTEL: I'm sorry, I just--maybe you can answer this--I thought these were not unopposed estrogens; this is not advocating unopposed estrogens.

DR. RARICK: No, in vasomotor symptom studies a woman can be enrolled with a uterus, and have unopposed estrogen for three months. That's where we are advocating at least two weeks of a progestin challenge at the end.

I wouldn't mind your comment on whether you'd want your vaginal ultrasound before or after the progestin challenge.

DR. LERNER: I'm the local ultrasound pro here, and it would clearly have to be after the withdrawal, I believe--yes.

CHAIRMAN AZZIZ: AGain, we're only concentrating on vasomotor symptom studies.

I am confused. Do we need to have ultrasound measurements? I don't agree. I mean--I'm sorry. Did you say, Richard, that in a three-month study we still needed to

do ultrasound? To do what?

DR. FALK: We're talking about a study. So I think this is different than a doc out in private practice deciding to give a person three months of estrogen to see what happens. For the purposes of a study where you're gathering data, I think for a relatively non-invasive, not painful, not terribly expensive test, it would be a reasonable thing to monitor for one of the known complications--albeit rare--at this stage of hormone replacement therapy.

CHAIRMAN AZZIZ: I have to disagree. I mean, I think that--I'm aware of the study situation, but the problem is this is potentially going to lead to more intervention than less intervention. I mean, I don't want to have the patients on the study undergoing fractional D&Cs or biopsies, or whatever it is, because they had a thickened endometrium, and a sonographer which happened to be a technician hired by somebody else on the outside and not an expert, doesn't know how to read these.

I mean, we need to make recommendations not because we just want more data on a study, but because it's useful or not. I think that in a three-month study, you may end up having more problems, because of poorly read sonography than less problem. Now, that's just my opinion, so I'd certainly like everybody else's opinion, as well.

DR. LERNER: Well, I don't know that anybody--the ultrasound experts have any particular cutoff that we've found to be helpful in that regard. So even if you used 5 mm, or 3 mm, or 8 mm--whatever you use, it's such variability that it's really difficult to come up with a number.

CHAIRMAN AZZIZ: Scary--that's all. But that sort of speaks to the same point, I guess. Thank you.

DR. LERNER: But I guess the other thing I wanted to say is just--you know, playing Devil's advocate here, I mean how many of our patients are going to be on the three months unopposed estrogen, get vasomotor relief, and then are not going to get on some sort of long-term therapy with some sort of different regimen. I don't know how much clinical applicability, you know, this will be, sort of in an isolated situation, to be used in this regard.

DR. RARICK: Yes, I would just point out that three-month studies of vasomotor symptoms are a pretty easy route for an indication for an estrogen product. To add a progestin for women with a uterus, you do have to do a one-year, hyperplasia-prevention trial to show that you've chosen the right dose of your progestin.

So we do have many sponsors that are very interested in originally coming in with a vasomotor study. Now, they can do their trials on women without a

uterus--that's always an option--but there aren't that many of those in the U.S. any longer to choose from that are, you know, hitting the menopause with moderate to severe vasomotor symptoms, etcetera.

But, I mean, your point is well taken that this is not real-world; that women, oftentimes, with a uterus, don't come to their clinician and get three months of estrogens alone, and then get treated. But in the clinical trial setting, to prove that the estrogen itself works, and that you've chosen the right dose of the estrogen, these are the kinds of trial designs that are more straightforward.

DR. LERNER: Then do we have the ability, or is there some sort of precedent, to change that? I mean, why is it three months, and does it need to always be that way?

DR. RARICK: You are well-equipped here to tell us that you think it could be done in two weeks, or four weeks, or that we should consider alternative designs that you might propose.

CHAIRMAN AZZIZ: I just want to caution the Committee, though, that--you know, vasomotor studies are relatively difficult to do. And so we can't ask for a six-month vasomotor study. It i true that if they get approved for vasomotor symptoms, they then are less--they're subject to less constriction, or less study demands than somebody who goes for endometrial hyperplasia prevention.

But I'm not sure that asking them to do a nine-month study, or a 24-month study, with and without biopsies, and so on, is a reasonable thing. I mean, that's the other issue. So--

DR. LERNER: No, I was actually thinking about making it longer, but I'm just new, and I'm naive, and you know, I am just sort of thinking of my own, you know, clinical applicability. And so--you know, I don't know how many patients, you know, are just going to fall into that three-month vasomotor symptoms, unopposed estrogen, and then what are you going to do with them from there?

DR. HAMMOND: I think that this is just a standard bio-assay. I mean, you're just trying to show efficacy, and that's all.

CHAIRMAN AZZIZ: Any further comments on number 2--question number 2?

I think you've gotten most of our impression as to the use of biopsies in a three-month study. We're all a little bit concerned about a sponsor who comes in and says, "All I want is vasomotor symptom relief. I do a three-month study," and we have no clue what the long-term impact of the drug is. And I'm not sure we can address it right now. But we are concerned about that. I mean, the Committee is concerned--all of us are.

I mean, supposing we get drug--new drug

X--estrogen. Bizarre--different kind of estrogen--and I come in and I say, "I'm just going to use it for treating vasomotor flushings. Give me three months." I treat 100 women for three months, and I get this approval on a drug that will be used for the next 12 years on the same patients. I want to know what's going to happen. We're concerned.

But I'm not sure that this is the forum to address that, necessarily. But I'm just--is there anybody that's not concerned on the Committee?

DR. RARICK: And we hear you--and I think we then get into a discussion of new molecular entities, where we would all agree that the safety database is much different than a three-month trial. And there are--the International Conference of Harmonization Standards for amount of exposure that we would expect in at least 100 women for a year, for example, versus run of the mill estrogens that we've been seeing for the last 30 years.

So we appreciate that reminder, that you're thinking if there really was something novel and new, this wouldn't be adequate anyway--and we hear you.

CHAIRMAN AZZIZ: Just to remind the audience that every so often, if anybody in the public has a comment, please certainly either raise your hand, stand to the side, speak to one of the staff or something of that nature.

We'll be happy to accommodate you.

Let's move on to question number 3. The Division is considering either deleting or requiring clinical trials to support the inclusion in labeling of three indications that previously were listed for estrogen drug products as class labeling. These indications are--quote--"Abnormal uterine bleeding due to hormonal imbalance"--close quote; quote--"Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure"--close quote; and--quote--"Vulvar and vaginal atrophy"--close quote.

Please comment on this proposal. If you recommend that clinical trials are needed, please provide recommendations for possible study end-point measurements for each indication.

Now, before we go into the discussion, I have a question for the staff. In the end, we've gotten letters, and presentations about osteoporosis. And I don't see the question on osteoporosis, so I'll include it in here on deletions and so on.

As I understand it, it was an error not to include osteoporosis under patient labeling; that was remiss, and it will be in bold type, and so on and so forth. The second osteoporosis deletion is that a large amount of data has been deleted from the physician labeling. Now it just simply says, "osteoporosis," and it doesn't go on to give

you all the other things.

I would like to put my two cents in that, and I'd like to stay on that subject until we clarify it, because that's really what the main concern of the presenters and so on and so forth has been; and that is that probably more information on osteoporosis, or at least recommendations, should be included--perhaps not the page-and-a-half that was in the '90 and '92, but certainly statements as to calcium intake; statement as to prevalence of osteoporosis; and statements as to silent disease--these kinds of things, because patients do read that. And, in fact, it's probably thing, other than vasomotor flushing, that we can actually use for patients to take something when they're not super symptomatic.

So I do think that my opinion would be to include more information on osteoporosis, both in the physician labeling and the patient labeling; perhaps not as much, on the other hand, as the page-and-a-half that you had before, because it was sort of--it was unbalanced. But I think you've gone too far the other way. But that's my opinion in that regard.

I'd like to hear Committee comments on that osteoporosis section first, before we get into anything else.

MS. SCOTT: Julia Scott. I concur.

CHAIRMAN AZZIZ: Very Well.

And does anybody else have a comment? No? I just don't--you know, I just don't--Lisa looks back at her residency and says I'm driving people. I hope not.

But, anyway--let's--moving on to other--to this labeling issue and indications. What is the feeling of the Committee in regards to these three indications? Should they be put back into the labeling? If so, should we ask for clinical trials, and so on and so forth?

DR. RARICK: Can I suggest maybe starting with what I'm hoping will be the easier discussion?

We've put all three here, but we have different levels of what we're hoping for. For example, "c) vulvar and vaginal atrophy," which has existed in class labeling for a long time. If you think it's still an appropriate end-point--if that's your conclusion--I'm going to clarify the question for that one. What end points would you want to see? What is it--cytological changes that are estrogen-related? Or symptomatic relief? Or a combination? Or do you just think the indication's not necessary at all?

It scares me to remove it completely, because there are products that are specifically, only for vaginal and vulvar atrophy. But we lumped it here because it has the same idea--if you think it still remains, what are the end-points to use?

DR. FALK: I think symptomatic relief would be just perfectly reasonable for that. I don't think people treat vulvar or vaginal atrophy in the absence of clinical symptoms. So I think--you know histological, cytological study need be necessary.

CHAIRMAN AZZIZ: I have to disagree with Richard--today. In fact, many of these products are vaginal, and some of them are oral. There's a placebo effect. I still think you need to demonstrate some cytologic change; a maturation index is a fairly appropriate way of doing it. So I disagree that symptoms alone, in such a subjective area is not sufficient.

DR. DATTEL: The only other comments--there are pediatric indications for the use of these, that don't have--will have to do with atrophy of a different sort. And that--I don't know if that's included in this, or consideration; and also other non-menopausal uses for vaginal estrogen preparations--for example, post obstetric trauma, to prevent adhesions; things like that, where you would not use--

DR. HARRIS: Yes, it seems that there's an inherent conflict. You have a definition that's fairly stringent, describing menopause, and then under "b" and "c" you have--at least under "c," the physical manifestations of menopause, and "b" sort of a different way of describing

menopause, and then asking if menopause, or menopausal findings are a valid indication for the treatment of menopause--unless I'm looking at this wrong.

So, it would seem to me that if you say that the agents are indicated in symptomatic menopausal women, vasomotor symptoms are part of that, but certainly physical changes--vulvar and vaginal atrophy, and secondary problems with urination and/or sexual function would be an important part of rectifying the issues of menopause. And, again, hypoestrogenism--sort of a generic, overall statement about what menopause is--or a different way of expressing it.

DR. GREENE: Ricardo, I don't--Mike Greene--I don't understand why you're concerned about a maturation index. I appreciate the placebo effect, but if these are placebo-controlled trials, and you demonstrate efficacy over and above placebo, I see no problem with that.

And I would agree--and I would even broaden, specifically "c" to include non-specific urinary tract symptoms, which are well-known to respond--the distal urethra is estrogen responsive.

DR. FALK: I would agree with that--both--to the two comments. And I would also just point out that you demand any kind of objective hormonal confirmation for hot flushes--relief of hot flushes. So that I think that this would be consistent with that.

CHAIRMAN AZZIZ: Perhaps that is what bothers me. I mean, when we talked about vasomotor symptoms, I did think that we needed to have some hot flushing, and the same thing here, because this is a mechanism-related; I mean, what is the mechanism? Again, it should be proliferation of the epithelium.

So perhaps I am simply bothered by the fact that none of this requires any kind of objective data, both vasomotor symptoms, which I asked earlier, and epithelial changes. And I--my suggestion--of course it's a disagreement--is that there be some objective measurement.

But I have to agree with Dr. Harris that you can't treat menopause and not treat vulvar and vaginal atrophy. I mean, this is not--not correct.

DR. RARICK: But you can treat vulvar and vaginal atrophy and not treat menopause. You can use local therapies, or doses that are effective for vulvar and vaginal atrophy that may not be effective for other indications in the menopause. So you're right on the converse.

We would always believe that if you got systemic levels of estrogens that were appropriate for vasomotor symptoms, you would--quote--"automatically" be treating vulvar and vaginal atrophy. That's why it was a class indication.

There is actually quite a bit of data about patients who are relieved for their vasomotor symptoms, and are not relieved at the vagina and vulvar level--and vice versa. There are lots of therapies that are only for local therapy, and don't expect to get indications for system--you know, for more--you know, vasomotor systems, or other systemic sorts of manifestations.

We think--we have believed that they are separate. Currently our policies have been in the vulvar and vaginal arena to do both of your recommendations--both symptomatic relief, and some cytological confirmation. But we wanted to hear the discussion. And I can hear some push for--if you treat the symptoms, if there's a placebo effect, you just have to show that you're better than the placebo--that should do it. Ricardo wants to see some other evidence.

DR. GREENE: Ricardo, what you're objecting to as not being objective I would say is not laboratory, but could still be objective. You know, a woman can keep a diary, or whatever. That's still objective, even if it's not laboratory.

CHAIRMAN AZZIZ: Just for a point of clarification to Lisa--I mean, when we're talking about these indications being deleted, it's deleted from the general category, but they still remain as a possible indication for a manufacturer or a sponsor to come in and say--see, this is

what we're, I guess--why we're having a little bit of round discussion.

I think our feeling--at least with "e" and we'll go--with "c" we'll go according to the others--is that you should retain vulvar and vaginal atrophy. Now, whether you give that automatically as an indication to anybody who treats menopause, I agree with you that today we know that one doesn't treat the other and vice versa, and that if they are going to go for that indication as well, they should have a study, or a piece of data suggesting that.

But on the other hand, that is an indication that should be retained; that's pursuable. I think that's what we're--all of us are agreeing.

DR. FALK: I would just like to jump in, and at the risk of being pedantic, say that you don't treat menopause. You can't treat menopause. The only way to treat menopause is to make a woman ovulate again. And it's not going to happen--at least not so soon.

So you treat the symptoms of menopause. And that's why I get back to my original definition of "symptomatic hypoestrogenism," and therefore it's perfectly reasonable to treat these things with various methods.

DR. RARICK: Okay, let me understand. So far I'm hearing that you would agree that vulvar and vaginal atrophy, for example, is a definite indication. It's not

necessarily given automatically to an estrogen product that gets the vasomotor indication, for example; that a second trial would be necessary, or some subset of the first trial, to show something about the vulva and vagina, whether it be symptomatic or a combination of symptoms and cytology.

Again, just historically--just so you know--all three of these were often granted in the sort of automatic style if something was shown to be an estrogen for vasomotor symptoms. So we're simply trying to clarify with you. We have been treating vulvar and vaginal atrophy the way you've described, which is to ask for evidence in--for a sponsor to show us, from either their vasomotor symptom trial or a second trial.

The other two, then--we'll be curious as to how you would propose. And, again, you're right--if you want to, you could say, "We don't want them to be automatically given, but we think they could be obtained." Or you can say they should be automatically given, or "We don't know how you would obtain them."

DR. LERNER: Yes--I think it should not be automatically given, but if you want to specifically have that recommendation, then you need to do the studies to support that for each of whatever the areas that you're talking about.

CHAIRMAN AZZIZ: I'd like to hear--so we can get a

sense of the Committee and we can move on--does anybody disagree, on the Committee--disagree with our recommendation that this indication shouldn't be automatically given to an estrogen product, just because it--quote--"treats menopause?"

DR. HARRIS: Yes, I do disagree. You know, I think we're partitioning a disorder, and asking the manufacturers to show that for each target tissue there is an effect; show that there's an effect on the vasculature, show there's an effective vaginal and vulvar mucosa, show there's an effect on another target tissue. And I think that's really splitting hairs.

If we agree that the issue is really estrogen deficiency, and that there are target tissues that are adversely affected by estrogen deficiency--there may be a matter of degree, and there may be some statement of that. But, you know, in the absence of some prohibitive risk of, say, vulvar or vaginal therapy, or general hypoestrogenism, I don't know why we would need to do that. I don't think we do that with any other disorder when we agree that a specific intervention treats a specific disorder.

DR. FALK: I also disagree with that for the same reasons.

DR. LERNER: But I think that I agreed because I think that to try and clump all the estrogens--the topical,

vaginal estrogens and the oral estrogens are two very different categories, and to try and clump them all in the same breath, you know, may not do anybody any good.

CHAIRMAN AZZIZ: Umm--

DR. LERNER: That's why I disagree with the disagreeing.

CHAIRMAN AZZIZ: The only problem is that there are products out there that are designed only for vasomotor--for vulvar atrophy, and are not designed for--quote--"menopause," and there are products that are designed for vasomotor symptoms that don't treat the vulvar atrophy.

So, although I agree with you they should treat, but they don't, and that's unfortunately the reality of the marketplace.

Any other comments about this so we can move on? Okay.

Did you get enough information on that point? Do you need more clarification, Lisa? Okay.

Let's move on to b: hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

Comments on that, please.

DR. RARICK: Can I jump in, because I know that Dr. Harris and others have mentioned that this is just another definition of menopause. If we look back

historically at this category--who knows what they meant when they wrote it--but it appeared to relate to patients with Turner's syndrome; other sorts of unusual situations of lack of ovarian function.

And, again, I don't know that there's a great amount of data about the appropriate doses for particular unusual syndromes. This was not, in its original entity in the '70s, as just another definition of menopause. It really was a different category.

And I didn't know if--this language may not fit anymore? Or if it does, tell us how.

DR. DATTEL: Bonnie Dattel.

It gets back to the earlier discussion we had about being too narrow in our criteria, because, as we've been talking about it, there are a variety of different indications. All of them have to do with low estrogen, whether you're a pre-pubertal child and adhesions, and you've got low estrogen in your vagina, or whether you're post-menopausal, or whether you have a congenital abnormality.

So I think it gets back to that original thing of too narrowly defining your trial.

CHAIRMAN AZZIZ: You may be splitting hairs. Again, in this statement, you have three things, really. You have hypogonadism, which is totally one type of

disorder, it may be due to hyperthalamic amenorrhea, it may be do anorexia nervosa. Castration, of course--most people really wouldn't even need to put that there anymore. We know that a castrated person is menopausal. I mean--so that probably doesn't need to be used anymore. Primary ovarian failure is menopause; it's primary menopause--early menopause--whatever you use. And certainly that word "primary ovarian failure," or "premature menopause" should be somewhere in the definition of menopause. I mean, there are number of causes for menopause: surgical castration, natural menopause, primary ovarian failure, or what we call "early menopause." I mean, there's a large number of causes of menopause. So I don't think you need to do that.

So the only one that really, I think, needs to be dealt with is this so-called hypogonadism; the individual who is--has anorexia nervosa, or simply has delayed puberty secondary to a hypothalamic pituitary dysfunction, who then requires--and that I don't think is--should be an indication, but I don't think it should be--I'm not sure how to do that. I mean--but that is totally separate. That's a separate, if you would, disease.

A comment from the Committee?

DR. FALK: I don't know if that was a typographical error or what. Hypogonadism, per se, just means, in the case of females, the ovary is

under-functioning. And it does not imply hypothalamic suppression. What Ricardo is referring to his hypogonadotropism, which includes--hypogonadism is the same as any other kind of ovarian dysfunction or failure.

Primary ovarian failure is not the same as menopause--again, to get back to that definition. Menopause is the cessation of menses--after the last menstrual period. And primary ovarian failure, they never has menses. So I mean, again--it's a definitional point of view.

So I would--if this hypogonadism refers to hypogonadotropism--hypogonadotropic hypo--amenorrhea, then I would agree with Ricardo that it shouldn't be included in that category.

DR. RARICK: Yes, I'll just clarify again that we're dealing with language that has existed from 20-some years, and we're trying--we would like to remove it. But we can't remove it just like that, since this was all done during a process in the '70s to make these terms real, and put them in class-labeling for 20-some years. And so--we hear you. And we're happy to remove some of the terms that are no longer appropriate. Sponsors that have these indications that we now ask them to remove may want to push--that, well, maybe they do have information on hypogonadism--tropism--and maybe they will get a special indication for a specific category in that larger term that

used be a sort of umbrella, as far as we can tell.

Does that help?

DR. HAMMOND: Well, if the question is, as I understand it, that we're just looking at clinical trials now, and we're saying that if someone has an indication for vasomotor symptoms, are we saying therefore that they would be adequate replacement for hypoestrogenism, or do we have to have a separate classification.

And I guess my question would be for this category of hypoestrogenism--I don't even--we'd have to have an end-point again. And is that vasomotor symptoms? Is that vaginal atrophy? Either way, it may fall into one of these two categories. So I think perhaps if we have these two categories, we would cover this.

But for terminology, this is hypoestrogenism, which includes all these categories.

CHAIRMAN AZZIZ: Yes, I think the problem is a definition one. I mean, if you look at the broad category: estrogens to treat hypoestrogenism, and hypoestrogenism can be--occurs in these women because of hypogonadism--their ovary doesn't produce. Now, you can have hypogonadism due to ovarian failure, which would be hypergonadotropic, or you can have it due to hypothalamic pituitary failure, which is hypogonadotropic. But, unfortunately, estrogens will treat the symptoms in both. But that's why the ovarian failure,