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Parklawn Building
Conference Rooms G and H
5600 Fishers Lane
Rockville, Maryland
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Elisa Harvey, D.V.M., Ph.D., Executive Secretary

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Introduction

DR. BLANCO: We will start the meeting of the second day of this meeting of the FDA advisory committee on devices. I don't know the actual official name, but it is close enough.

[Laughter]

I would like to go ahead and call the meeting to order. I want to remind everyone in the audience that there is a sign-in sheet in the back of the room, if you would please sign in so we have a record of who was here, participating in the meeting.

We will have comments from the audience for the public record. Please raise your hand. You must be recognized by the chair. You must identify yourself; use the microphone so we can record what you say; and we need to have you state your name and give any conflict of interest disclosures, such as any payment for travel, per diem, or any involvement with any companies that are involved in the subjects to be discussed.

Having said that, let's go ahead and have the panel introduce itself. I am Dr. Jorge Blanco. I am a Professor and Associate Chairman of the Department of Obstetrics and Gynecology at the University of Florida, Pensacola, Florida, and Medical Director, Sacred Heart...
Women's Hospital in Pensacola, Florida.

DR. NEUMANN: My name is Michael Neumann. I am a Professor in the Biomedical Engineering--Joint Program in Biomedical Engineering--it is a new program and I am having trouble remembering the name, at Memphis, which is a part of the University of Tennessee, Memphis, and the University of Memphis. I also hold adjunct appointments at Duke University and at Case Western Reserve University.

DR. ROY: I am Subir Roy. I am Professor of Obstetrics and Gynecology at the University of Southern California School of Medicine.

MS. YOUNG: I am Diony Young. I am the consumer member of the panel, and I am editor of the Journal Birth, and I live in Tennessee or New York.

DR. YIN: Lillian Yin, Director, Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices with the Center for Devices and Radiological Health, FDA.

MS. DOMECUS: Cindy Domecus, Senior Vice President of Clinical Research and Regulatory Affairs for Conceptus, and I am the industry rep. on the panel.

DR. CHATMAN: I am Donald Chatman, generalist in private practice, in Chicago, Associate Clinical Professor of Obstetrics and Gynecology at Northwestern Medical School, and Vice Chairman of the Department of Obstetrics and
Gynecology Michael Reese Hospital in Chicago.

DR. SHARTS-HOPKO: I am Nancy Sharts-Hopko, Professor, College of Nursing, in the field of maternal, infant and women's health, at Villanova University, Villanova, Pennsylvania.

DR. SHIRK: I am Gerald Shirk. I am a private practitioner in Cedar Rapids, Iowa, and Associate Clinical Professor at the University of Iowa.

DR. KATZ: I am David Katz. I am Professor of Biomedical Engineering and Obstetrics and Gynecology at Duke University.

DR. HARVEY: I am Elisa Harvey, the Executive Secretary to the Obstetrics and Gynecology Devices Panel, FDA.

DR. BLANCO: All right, let's just go over a few points of information. We have a very full agenda today so let's make sure that if you have any comments, that they are brief, concise and to the point. If we are looking for some data, please provide the data and not the opinion, and please let's not have any outbursts. Hopefully, it is not going to be that controversial.

I would like to turn over the meeting now to Dr. Harvey, who will read some of the information. Before I do that, the FDA press contact this morning will be Dr. Yin, right at the end of the table.
DR. HARVEY: I would just like to read the conflict of interest statement for today's meeting.

The following announcement addresses the conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Waivers have been granted to Drs. Donald Chatman and Subir Roy for their financial interests in firms at issue that could potentially be affected by the panel's deliberations. The waivers permit these individuals to participate fully in today's discussion. Copies of these waivers may be obtained by the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Dr. Nancy Sharts-Hopko. This individual reported interests in
firms at issue, however, on matters not related to today's deliberations. Since these interests are not related to the specific issues before the panel, the agency has determined that she may participate.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

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

I would also just like to point out that if you are interested in transcripts or videos of today's meeting, there are handouts at the sign-in area that you can take. If there are any presenters to the panel who have not already been in touch with me, they should provide a hard copy of their remarks and overheads. Mr. Yung Pak, if you could stand up—you can provide those to him.

I would just like to note for the panel what their folder contents contain. You have an afternoon session as well. Your morning session materials are on the left side of the folder and your afternoon is on the right.
DR. BLANCO: Thank you, Dr. Harvey. At this time, it is our pleasure to introduce Mr. Colin Pollard. Mr. Pollard is the Chief of the Obstetrics and Gynecology Devices Branch, Center for Devices and Radiological Health, Rockville, Maryland. He will be making an introduction and general updates, and providing a brief overview of the purpose of this panel meeting.

Introduction and General Updates

MR. POLLARD: Thank you, Dr. Blanco. Members of the panel, distinguished audience, this morning we have asked the panel to look at endometrial ablation devices again, this time in a generic way in the context of a guidance document.

As you know, FDA and the panel has been very actively involved in reviewing the progress of a variety of new types of devices used for endometrial ablation. Following a panel meeting that we had in 1995, FDA developed and issued a guidance document to assist manufacturers in preparing IDEs and PMAs for these kind of devices.

In that context, we set up a variety of definitions for those kinds of studies, including the type of women to be studied. In this case it was premenopausal women; the diagnosis of abnormal uterine bleeding and the context of failed hormonal therapy; a scoring system and
quality of life indicators; and the time frames for studying that, including three months pretreatment and then the follow-up, six months, one year and up to three years.

We expect that in these past three years we have learned a lot. We expect that we are going to be updating that guidance document and improving it based on two or three panel meetings that we have had since then.

More recently, we have seen interest in using these kinds of devices to treat postmenopausal women under hormonal replacement therapy who are experiencing refractory bleeding. We are not sure that the current guidance document really adequately addresses that new indication, and whether or not there are aspects of it that do apply, or other things that should be folded into the guidance document to address this new indication, and those might include what the definition of an appropriate surgical candidate would be; the hormone replacement therapy regimen to be followed before turning to ablation; the appropriate endpoints to be studied; the follow-up period; and even aspects with respect to the device design.

Towards that point, the FDA staff has crafted a set of discussion questions that we are asking the panel to look at and give FDA comment back so that we can update our guidance document for this new indication. Dr. Diane Mitchell, the OB-GYN reviewer in our Branch, will be
presenting those questions to you but, before we do that, I think we are going to have the open public hearing first and after that Dr. Mitchell will introduce those discussion questions. Thank you.

DR. BLANCO: Thank you, Mr. Pollard. At the current time, there are no registered speakers from the public that we have on this particular item. Is there anyone in the audience from the public that would like to make a comment concerning the deliberations before the panel?

[No response]

If not, we will proceed on with the agenda. At this point, Dr. Diane Mitchell, of the Food and Drug Administration, will present the questions to the panel.

Open Committee Discussion

DR. MITCHELL: Good morning. Dr. Harvey, what do you think would be the best way for me to present these questions, or Dr. Blanco? Read them all? One at a time?

DR. BLANCO: I don't know how many you have this time. Why don't you go ahead and do all of them at first, and then we can go back and see what we will do. So, go ahead and do all of them.

DR. MITCHELL: All right. Some postmenopausal women on hormone replacement therapy experience refractory troublesome uterine bleeding. Even after adequate hormone
replacement therapy management, some of these women still manifest such bleeding. Hormone replacement therapy is currently indicated for osteoporosis and vasomotor symptoms.

Question one, what is the right population of postmenopausal women on hormone replacement therapy to treat with endometrial ablation? Please comment on the following:

What constitutes refractory troublesome bleeding?

Comment on bleeding patterns and durations.

What are other important indications for intervention?

What are the essential components of a pre-intervention medical therapy algorithm for bleeding after three months of hormone replacement therapy?

Question number two, what is the appropriate patient work-up to rule out preexisting or coexisting pathology that may precipitate refractory bleeding?

Comment on the role of endometrial biopsy; transvaginal ultrasound; hysteroscopy, both diagnostic and operative.

Patient characteristics—should any of the following patient characteristics influence the inclusion or exclusion criteria for a clinical study of endometrial ablation for postmenopausal women on hormone replacement therapy? Specifically, age, perimenopausal status, dosage of estrogen, dosage and type of progesterone, uterine size,
1. history of successfully treated hyperplasia, risk factors for endometrial cancer such as obesity, smoking or associated conditions, and other.

Question three, what should the primary study endpoint be: reduction in bleeding versus amenorrhea?

What role should secondary endpoints, such as quality of life indicators, play in clinical study design for postmenopausal endometrial ablation?

Question four, do specific device design considerations or thermal modalities require feasibility studies for the postmenopausal application?

DR. BLANCO: Thank you, Dr. Mitchell. At this time, the meeting is open for discussion among the panel members. Would any panel member care to begin the discussion on question one? No takers?

I will start. I have a viewpoint. The first question is what is the right population of postmenopausal women on hormone replacement therapy for treatment with endometrial ablation? I am a little bit concerned about the utilization of this particular procedure on postmenopausal women. There is a significant number of studies, at least three, that show that most of the women who have postmenopausal bleeding--a significant number, I think in one it was 85 percent--have it from endometrial polyps, myomas or some other cause that is unlikely to be treated by
the endometrial ablator.

So, I am not sure why we want to say that this is an indication for it. So, having thrown that out, does anybody feel differently? Dr. Shirk, you were going to make some comments.

DR. SHIRK: Well, I think there is certainly a subgroup whose life quality is improved and, again, I think this is a life quality issue. Certainly there is a group of women who have--there are really two groups of women: a group of women who have heavy menorrhagia if you put them on cyclic programs, and probably historically they have heavier than normal periods throughout their life. So, they just don't wish to continue to have heavy periods, although they would tolerate a cyclic program.

There is another group of women who probably had adenomyosis when they were premenopausal, and they just simply activate adenomyosis again with these women, and they have this same kind of abnormal bleeding patterns that you would see in those patients with adenomyosis. I would think a significant number of patients that we treat premenopausally with endometrial ablation are patients who really have superficial adenomyosis as a diagnosis, and I think if you go back to some of the studies, you know, where biopsies were done you would note this.

So, yes, I think there is a subgroup of women who,
you know, will continue their hormone replacement therapy, and the argument is basically should those patients be offered this technology as a means of allowing them to continue their hormone replacement therapy, otherwise they are going to discontinue their therapy, which is probably not in their best interest.

DR. ROY: Well, I think it depends on what the schedule of hormone replacement therapy is, and whether it is acceptable, as Dr. Shirk said. If you are giving cyclic therapy and you are expecting periods, and those periods are heavier than the woman is willing to tolerate in order to continue, and she would discontinue unless you did something then, of course, this might be an appropriate choice. On the other hand, if you are trying to give her combined continuous therapy, trying to diminish her irregular bleeding rate and she discontinues because she can’t find a dose of estrogen and progestin to accommodate that, then this would also be a potential suitable cohort, removing those factors that Dr. Blanco said, like polyps or fibroid, or things like that.

DR. CHATMAN: I think that there is no question that there is a group of women, who are postmenopausal who have abnormal bleeding, who are suitable for this technology, and whether or not we like it, it is going to be applied. The question I think is, is it safe? Is it safe
because the uterus is atrophic, small, thin? Is it safe
with reference to the issue of endometrial carcinoma
becoming an occult disease in patients of this type, and
being diagnosed late and, therefore, treated late and
suboptimally?

The safety issue I think is the one that we need
to--obviously effectiveness is important too but I think we
know something about that. We probably don’t know enough
about the effectiveness of endometrial ablation in
postmenopausal women because I don’t know that we have
enough data to say whether or not it is effective as yet.
But I think the safety issue is the primary question here.
I don’t think there is any question that that is going to be
applied by some gynecologists because the American
population of females are going to demand it, and I think
rightfully so.

MS. YOUNG: Well, I can’t speak on the basis of
studies, but my own experience and talking with other women
in this age group that you are talking about, who could
conceivably fall into the subgroup, I think that the first
line of defense has to be manipulation of the hormone
replacement therapy schedule. And, this is something that
actually isn’t done always by physicians. Some women I know
have actually done their own investigations to look at a
variety of schedules, and actually come across a schedule,
and I will mention the one which I sort of threw out to my own obstetrician-gynecologist which was five days on and two days off. And, it was very interesting that that particular schedule eliminated the bleeding.

So, I think that, you know, that is the first thing that has to be considered. So, I think that any possible additional problems that there might be--lesions or whatever, everything has to be ruled out before one would consider this particular therapy.

DR. BLANCO: It is very obvious that the opinion of the panel seems to be that there is a subset of women where this would be useful. So, I think one of the things leading in from what Miss Young just said is let’s look at the rest of this question. First of all, what is refractory bleeding. I think the other issue is how do we define that subset and make sure that these other things are identified, and that time is not wasted utilizing this procedure when there is something else that needs to be done, and go from there. So, how should we look at troublesome bleeding, bleeding where this technology might be applied?

DR. SHARTS-HOPKO: I am inclined to think that you have to look at it. You know, it is like the definition of pain; it is when the patient says it is a problem. And, most women are not happy with any bleeding that takes place after the natural time at which shouldn’t, whatever that is.
[Laughter]

DR. BLANCO: All right, so your definition would be any type of postmenopausal bleeding that bothers the patient, which might make her at least initially eligible for that. Anyone want to comment on that?

MS. YOUNG: Yes, just let me say I agree. In fact, the issue of patient difference and patient concern, which gets back to the quality of life issue, that is important for that individual patient really has to be a major consideration.

DR. SHIRK: I guess my question there would be do we then offer it as essentially a cosmetic procedure, and how is it different than a normal patient who is forty years old, walking into my office and saying, "I don't like to have my periods; I want you to do an endometrial ablation on me to try to reduce or remove my periods?"

DR. CHATMAN: There is one very important difference, and that is maintaining hormone replacement therapy in these women. A lot of them will eliminate the medication to stop bleeding because they would rather not have the medication. There is no immediacy about taking the medication. So, a lot of patients that I know of in my own practice will stop taking hormone replacement therapy if the bleeding is not controlled. So, that is a big difference I think. What you are talking about is the totally elective
cosmetic procedure, and this is, I think, quite different because if we believe in hormone replacement therapy we are going to have to encourage patients to take it. This is one of the ways to do that.

DR. BLANCO: Right, and I didn't mean to imply that, you know, if you have troublesome bleeding you go to ablation. What I meant to imply is that whatever process is recommended, evaluating shouldn't be based on you have to bleed for so long or, what we were hearing from a couple of members of the panel, you know, if you are postmenopausal and you are bleeding that is not good. We all know it is not appropriate and needs to be evaluated. After an appropriate evaluation, which we will talk about in a minute, then this may be a procedure that may be utilized. So, it is not just bleeding and go to ablation; it is a little different. Okay? Anyone else have a problem with just postmenopausal bleeding, or do you want a pattern and amount? Subir?

DR. ROY: I am just having a little difficulty understanding why the FDA wishes to get involved in the algorithm as opposed to the device and its use, were there to be one, and how they would perhaps follow up. It seems to me that we are in the realm of the practice of medicine. As Miss Young mentioned, different practitioners practice it differently. Are we going to have a check list that says
that unless you have gone through the hoops that we hold out for you, you are not permitted to go forward?

DR. BLANCO: I am going to let Dr. Yin speak to that, but I think that is not the point. I think the point the FDA probably would like is some guidance on how to let the companies know what kinds of expectations, or what kind of study design they need to develop if they want to market it for a postmenopausal application.

DR. YIN: Exactly. Thank you, Dr. Blanco. That is exactly what we are facing. The manufacturers are asking if they have that particular claim what kind of studies they should have, and we are faced with the necessity and it is up to you to advise us if this is really medically indicated, or if it is, like you suggested, cosmetic, or how you are going to separate them out, or how you are going to propose that, yes, there is a subset and do it this way. Then we will work with the protocol.

DR. BLANCO: Yes, that is why I was sort of taking the devil's advocate approach. If everybody thought, well, there is no place for this, then it is over and we can all drink coffee for the rest of the morning.

[Laughter]

But if not, then we need to get to how do we identify that subset so that that subset can be identified and the companies can, you know, set up a study to utilize
it in that subset of patients. Dr. Chatman?

DR. CHATMAN: I wondered if anybody knew what the frequency of discontinuation of hormone replacement therapy because of bleeding is in a group of postmenopausal women. I think that is important.

DR. SHARTS-HOPKO: I believe, from a review article that I read in the last year, that the five-year continuation rate is less than ten percent.

DR. CHATMAN: That is for all reasons?

DR. SHARTS-HOPKO: For all reasons, yes.

DR. CHATMAN: I was talking about specifically bleeding. You know, bleeding in the postmenopausal period and hormone replacement therapy discontinued because of the bleeding. That is the group that I am looking at.

DR. ROY: Well, there is a multiplicity of reasons and, you know, any excuse will do. If you have breast cancer, bleeding, tenderness, all these things sort of fall together somehow. I don’t know that anyone has rigorously tried to characterize the specific reason why women discontinue but at least our clinical impression is that over fifty percent of those who discontinue do so because they either don’t want to continue bleeding if they are on cyclic therapy, or they despise the unpredictability of the spotting and bleeding that occurs with combined continuous therapies.
DR. BLANCO: Let me try to bring the committee panel back to the question at hand. I think the first issue to address is the issue of is it a cosmetic procedure or is it something that medically can be offered? Okay? Because I think that is the crux. If we agree that there is a subset of patients where this may be of benefit either to stop the bleeding or to stop the bleeding so that they don't come off hormones, either way, then I think we need to define how we get to that subset. But I am hearing that some folks think that maybe it is not that important. What is the opinion of the panel?

DR. ROY: I personally think it is very important because I think it is the predominant reason why women discontinue.

DR. BLANCO: Then let's proceed. So, essentially what I believe I am hearing, and let me know if I am wrong, but essentially any postmenopausal bleeding is troublesome and might result in a patient that could end up being a candidate for an ablation once appropriate indications or contraindications are applied. Right?

DR. CHATMAN: I am not following that.

DR. BLANCO: Okay. Just basically, there is a subset of patients whom this might benefit, and the idea is who is that subset and what needs to be done to make sure they don't have safety issues, as you brought up--the
endometrial cancer issue, and how do we get to identify
those patients. But there is a subset, and you would say
any bleeding would be troublesome. That is what I think the
committee is saying.

DR. CHATMAN: What I am saying is that those
patients who are on hormone replacement therapy who bleed
need to be encouraged to stay on hormone replacement
therapy. If endometrial ablation does that, then there is
an indication for it. I am not sure about the other.

DR. BLANCO: Okay. How about part (b)? What are
other important indications for intervention? I am not sure
where that question is going, quite frankly. Other than
bleeding, I don’t see what you would want to intervene for
with an ablation. Anybody want to comment? No?

DR. ROY: I guess some people have pain. That is
more associated with adenomyosis, and I think that is an
important distinction. If there is pain associated with the
bleeding, then perhaps other strategies could be
entertained. McCausland, out at UC at Davis, recommended
that prior to ablation a biopsy be taken, and if adenomyosis
were present that ablation not be entertained because it
wouldn’t adequately treat that symptom complex. So, I don’t
know whether that is what they are referring to. That would
be almost an exclusion, that if you found adenomyosis you
wouldn’t go ahead with attempting ablation.
DR. CHATMAN: It is unfortunate that you can't make a diagnosis of adenomyosis by simply biopsing the uterus. So, it is just not practical.

DR. ROY: Well, you can if you are lucky.

DR. CHATMAN: Yes.

DR. ROY: Well, there are certain characteristics, I guess, that have been suggested as predictive, and then if you biopsy that region with a resectoscope you can get actual tissue that is histologically confirmable.

DR. CHATMAN: We have found it to be very, very unreliable though. What looks like adenomyosis may not be adenomyosis, and I don't think it is predictable.

DR. BLANCO: Let's ask Dr. Mitchell. Maybe she can enlighten us a little bit more on this question. Are we understanding the question that FDA is posing to us correctly or appropriately? Or Mr. Pollard? One of the two.

DR. MITCHELL: Bleeding, of course, is the primary indication. The second question was just specifically if there was anything else of issue that should be entered into the decision-making, and I don't have anything specific, except to reinforce the idea that what we are looking at here is the risk-benefit ratio, and we want to make sure that for the patients who do receive endometrial ablation that the benefit of the procedure will outweigh the risk.
DR. BLANCO: All right, I think we can move on to (c) then. Go ahead.

DR. ROY: The other way to look at this is that we are considering ablation as opposed to, say, hysterectomy. If you had genuine stress urinary incontinence, significant descensus, symptomatic cystocele or rectocele, dyspareunia, problems with defecation, then you wouldn't necessarily consider ablation in that individual unless there was some medical reason why you couldn't take her to the more definitive--maybe we shouldn't use "more definitive" but at least the surgical approach for the treatment of that condition. So, in the absence of those parameters, then ablation could be considered.

DR. BLANCO: So, in the absence of an indication for more generalized surgery ablation may be a modality to utilize in a subset of patients.

All right, let's move on to (c). What are the essential components of a pre-intervention medical therapy algorithm for bleeding after three months? So, essentially a patient is on hormone replacement therapy three months; comes to see you and complains about bleeding; you are going to manipulate her hormones.

Obviously, what we are looking at here, again, is not for the FDA to dictate medicine; what we are looking for is who would be a candidate for that subset of patients for
whom we said endometrial ablation might be useful, and what should the requirement be for hormone manipulation, if any, before they would be candidates? Anyone want to tackle that?

DR. SHIRK: Well, I think obviously you have to preclude before that an essential medical work-up, which is the next question, but I certainly think that probably we are going to have to define how many different attempts. I mean, are we just going to go straight to ablation or, you know, how many different modalities of hormone replacement therapy to try to solve the patient's problem are adequate? I would say that certainly at least two or three different dose changes would probably be appropriate before the patient is considered for ablation.

DR. BLANCO: Yes, I don't think you can be specific because there are so many hormone replacement therapy modalities that a patient can be put on --

DR. SHIRK: Right.

DR. BLANCO: --so how many changes should occur in hormone replacement therapy prior to the woman being a possible candidate for ablation? And, you would say two or three? What do you think, Don?

DR. CHATMAN: I would say six.

DR. BLANCO: Six? You know, I would go the other way. I am just being a devil's advocate--
[Laughter]

--I mean, what kind of number? We are talking about numbers here. I think what we should say is something to the effect that we should have some effort at manipulating hormones to effect amenorrhea. We can't talk about numbers, I don't think.

DR. SHIRK: I think yes and no. I think if you are looking at it from what a practical physician is going to do, I agree with you, no. But if you are looking at it from what we should require of a company study, in other words, before patients are included should there be a number? And, I would have a tendency to say there should be, yes, some manipulation of the hormones because I wouldn't want it to be too long because I think the patient is just not going to come back to you. You know, I think even two or three times--"hey, I'm tired of this bleeding. I don't care what hormones are the next ones; I'm not going to come back."

MR. POLLARD: I just wanted to make two comments, one with respect to the discussion that is going right now. We probably have to differentiate a little bit between what is an appropriate interventional approach to take here versus if you are going to do a clinical trial what kind of standardization should be made so that the information that you get at the end of the day has some kind of, you know,
predictability as to the effect of the device. I think that
is some of the flavor of question 1(c).

The other thing that Dr. Yin just mentioned to me
that I don’t think we actually said at the beginning of the
meeting is that there will be a period of time a little bit
later this morning where the audience will be given an
opportunity to comment on the deliberations, and I just
wanted to make sure but, you know, that is kind of at Dr.
Blanco’s discretion, when a good point is to do something
like that but just so that the audience knows that.

DR. BLANCO: Well, I think we probably ought to
try and get through the questions first, and then see if
someone has major problem with any of the discussions that
we have had so that we can go over it.

DR. CHATMAN: Are we designing a study for the
companies?

DR. BLANCO: I think we are advising FDA on what
the requirements should be if a company wants to design a
study. I think that is question number five, the bottom
line. Yes, Dr. Shirk?

DR. SHIRK: It seems to me that we really ought to
answer question number two before we come back and answer
(c) in number one because, I mean, basically the question is
if you get a patient who is postmenopausal on HRT, basically
how should you react to that, and after you have reacted to
that and worked the patient up appropriately and ruled out
every other pathology that is causing it, then how would one
proceed with hormone manipulation before the patient then
becomes a candidate for endometrial ablation, which is, to
me, the more logical approach to the problem?

DR. BLANCO: Again, we are not dictating how a
physician wants to do it. What we are doing is giving
advice as to what should be included in the study.

DR. SHIRK: Right, but, you know, these are
obviously the patients who have pathology that has to be
treated and are, you know, obviously out of the study, and
then we are down to a subset of patients who have bleeding
with a normal uterine cavity, and how much manipulation
beyond that is important before those patients are selected
as a group of individuals that are candidates for a study.

DR. BLANCO: Well, you have the floor. Why don’t
you start on question two? That is perfectly fine.

DR. SHIRK: Okay. I think the big issue with
work-up of patients in a postmenopausal range is that
historically the OB-GYN and medical community in general has
been programmed to ask one question, and that is does this
patient have endometrial cancer or not. So, they basically
ask only that question. They don’t ask the question as to
why is this patient bleeding. I would say that ninety
percent of gynecologists who see a patient--and that
certainly would be substantiated in my practice because we did a big study on this in our practice a couple or three years ago--basically are just going to do an endometrial biopsy on this patient and say, "no, you don't have precancerous or cancerous lesions so let's start manipulating hormones," which doesn't really answer the question of why is this patient bleeding. So, the answer is that obviously endometrial biopsy is one of the important questions but doesn't answer the real question.

DR. BLANCO: Well, what should they be asking?

DR. SHIRK: Basically we need to go back to our original thing with endometrial ablation, that these patients either have to have a saline infusion sonography or they need a hysteroscopy for complete evaluation of the endometrial cavity.

DR. BLANCO: But you wouldn't disagree that if the biopsy showed cancer that would still be an appropriate step.

DR. SHIRK: No, if I have answered the question as far as why is the patient bleeding.

DR. BLANCO: Right.

DR. SHIRK: But, I mean, there are a lot of other things besides cancer.

DR. BLANCO: But it is part of that issue of, you know, before we would do an endometrial ablation we would
want to make sure that there are not polyps, submucosal
myoma or something else that could be the reason for the
bleeding that we know is a high percentage of the reason for
the bleeding in this population.

DR. SHIRK: Right. And, I think it is really
doubly important in this group of patients that, you know,
we stress that in a study because it needs to be stressed if
the general population is going to use this because there
are going to be a lot of people out there just simply doing
endometrial biopsy, if it is approved, and then basically go
straight to endometrial ablation without even looking.

DR. BLANCO: So, an endometrial biopsy is not
sufficient. It will tell you if there is cancer but it
won’t tell you if there are polyps or any abnormalities in
the cavity.

DR. SHIRK: Right.

DR. BLANCO: Now, you mentioned saline infusion
ultrasound and hysteroscopy. Should it be one or the other,
or both? Do you need a biopsy as well if you are only going
to allow the saline infusion?

DR. SHIRK: Oh, I think biopsy plus one of the
other two.

DR. BLANCO: So, saline infusion or hysteroscopy
and endometrial biopsy to rule out carcinoma or precancerous
lesion. Comments? Dr. Chatman, do you agree with that?
DR. CHATMAN: It sounds fine to me.

DR. BLANCO: Good. All right, so that would be part of the work-up. Is there anything else you want to do in the work-up of these patients?

DR. SHIRK: I think the main thing is just to make sure they don't have any intrauterine pathology so I don't know what else you would do.

DR. ROY: Well, any systemic disease that could impact the hematopoietic system and things like that. That would be a routine screen in the history and basic underlying lab tests, but apart from that, as Dr. Shirk said, it is intrauterine pathology.

DR. CHATMAN: Just looking at the Ray Valle study, it suggests that diabetes should be an important parameter to rule out.

DR. BLANCO: Okay, in the design of the studies should diabetics, because there might be a higher risk for endometrial cancer, not be included in a study for ablation do you think, or would a biopsy be sufficient to rule that out for you? Give us more information. I am not sure I know where you are going with the diabetes. What do you want to do with the information if they are a diabetic?

DR. CHATMAN: Well, I think it needs to be taken into consideration certainly because, evidently, it is a fairly significant factor in the development of endometrial
carcinoma in patients who have had ablations.

DR. BLANCO: So, would you use that as an exclusion criterion for endometrial ablation if everything else was okay? Or, would you require more than a biopsy of the endometrium?

DR. CHATMAN: I am just, you know --

DR. BLANCO: I want to see where you are going.

DR. CHATMAN: I understand what you are doing; I just don't know the answers.

MS. DOMECUS: I think we have to be really careful about writing exclusion criteria for the study because it does usually affect the final labeling. So, then diabetics would be excluded from the final labeling.

DR. ROY: And they may be the very ones for whom this procedure--because of other medical reasons, this might be more suitable. So, I think the question is that it should be asked and answered and recorded so that we know down the road, in the three-year follow-up or whatever, exactly what transpires and whether that was and continues to be a factor that is linked to hyperplasia, or failures, or cancer development, or whatever.

DR. SHIRK: I would think the big question is basically, you know, what constitutes medical risk for endometrial cancer in these patients. I guess if you go back to Sitiri and Bob McDonald's original article which
showed that high estrogen levels play a major role in developing endometrial cancer, back in 1970, basically when they looked at all the populations, basically obesity is the problem, not the diabetes and not the hypertension. It is basically the production of estrone peripherally, the high estrone levels that these patients have that is the high risk for endometrial cancer. So, I mean, it is pretty hard to start putting other medical diseases in as risk factors, I would think, I mean, unless you just want to lump obesity in as a factor.

DR. BLANCO: Well, I don't think that where Dr. Chatman or Dr. Roy were going was that that was an exclusion. As a matter of fact, I think what they are saying is that as part of the study you want to follow the obesity, and probably obesity should be included as well, and you still want to exclude carcinoma or a precancerous lesion but you want to follow that because we don't know if maybe in those patients ablation may actually lower their risk by getting rid of the endometrium, a significant portion of the endometrium, and actually be more beneficial. So, I don't think that is where you were going, was it, Subir?

DR. ROY: Right.

DR. BLANCO: I mean, it is just a matter that that needs to be followed to see whether it is detrimental or
I guess the question that I was going to ask Dr. Chatman or anyone else is that we know that with an endometrial biopsy we don’t sample a significant amount of the endometrial cavity. Okay? In patients that are at high risk before going to this procedure, like diabetics, should we do more than an endometrial biopsy, or should the requirement be the same? I don’t know; I am just seeking opinions.

DR. CHATMAN: An initial D&C doesn’t do much for them in terms of biopsy. You could require hysteroscopic evaluation of the endometrium with directed biopsies.

DR. BLANCO: Or, do you think that is necessary because that could be the issue. I mean, maybe the patients that are at high risk need a hysteroscopic rather than a saline infusion and biopsy, or is a saline infusion good enough?

DR. SHIRK: I think you can see endometrial thickening as well or better on saline infusion sonography, and you can certainly do, you know, point biopsies on saline infusion sonography. So, anybody who does a lot of high level sonography is going to argue basically that hysteroscopy and saline infusion sonography are going to be one to one in quality.

DR. ROY: But if you are going to use that are you...
going to make a distinction that the endometrial echo complex be above a certain amount or be uniform, and if it is irregular then those individuals should have further evaluation?

DR. SHIRK: Is that a clinical judgment, or do we want to put that in as a guideline?

DR. BLANCO: Well, again, we are trying to give them guidelines for what the studies should be, and I think the point is that if you have a saline infusion ultrasound or hysteroscopy that makes you think that this patient may already have significant disease like a cancer or a precancerous lesion, do you want to ablate those when you are thinking that this is a high possibility? That is a little different than just being obese or a diabetic and being at risk because of that and now you have a specific lesion possibly.

DR. SHIRK: But the question is basically whatever we apply to the study would be applied criteria after the study to general use, and so obviously you then significantly limit general use by saying that all these patients have to be studied by hysteroscopy. In the future, essentially most of these patients are probably going to be studied by sonohysteroscopy. So, I still think it should be included in the study because that is in general how most of this is going to be handled when it is in general use.
DR. BLANCO: No, I don't think Dr. Roy was arguing that it shouldn't be included. I think what he was saying was that the whole point of hysteroscopy or saline infusion is to look to make sure that you don't have a situation where you are more than at high risk for an endometrial carcinoma or precancerous lesion but that you have enough suspicion that you want to do something else. Am I reading that right?

DR. ROY: Yes, that is right. I am actually asking for how you manage your patients. When you do the biopsy and they continue to bleed you do your vaginal-probe ultrasound with or without saline. I take it you are more inclined to do it with saline. But let's just suppose that you did the endometrial echo complex assessment and it was completely uniform, and you saw it well and it was less than 5 mm. Would you then do sonohysteroscopy?

DR. SHIRK: No. But then the question is do you need a biopsy? If you have an endometrium certainly below 3-4 mm or certainly 3 mm and you look at it, you can argue that you don't even need to do an endometrial biopsy. The incidence of endometrial carcinoma in those patients is so low that biopsy is no longer required.

DR. BLANCO: I am not so sure about that--

DR. SHIRK: Well, but I mean that is the way the world is arguing right now, that if you do a
sonohysteroscopy and it is below 5 mm thickness, you don’t even need to do an endometrial biopsy any more.

DR. BLANCO: So, the first you do is a sono, a vaginal-probe ultrasound.

DR. SHIRK: Right.

DR. BLANCO: With saline?

DR. SHIRK: Not always.

DR. BLANCO: So, the first step is you do the ultrasound--

DR. SHIRK: Right.

DR. BLANCO: If it is below a certain amount you don’t even do a biopsy--

DR. SHIRK: Correct.

DR. BLANCO: But if it is above what amount do you then do the saline sono?

DR. SHIRK: If it is above five, then we do the sono.

DR. BLANCO: Okay, and if that evidence is some atypicality that is an irregularity, then you go to a hysteroscopy?

DR. SHIRK: Right.

DR. BLANCO: Okay. So, maybe that is the algorithm to ask for, for the company protocols. All right, hopefully, that was as clear as mud for the FDA!

[Laughter]
How about other things? We talked about saline infusion, hysteroscopy and biopsy. We talked about making sure that we note obesity and diabetes. Should we note other medical complications to follow those up, and are there any patient characteristics--we are now kind of addressing (b). Are there any patient characteristics that we should take into account?

DR. SHIRK: What about an ultrasound for evaluation of possible ovarian masses because you can have, obviously, problems with patients who have estrogen secreting ovarian tumors that show up in this group?

DR. BLANCO: Okay, being the case of the bleeding. Anything else? So, we want to make sure to do a good pelvic exam and ultrasound to make sure that we don't have ovarian mass that may be estrogen producing. Don, you don't seem to agree with that. Do you think that is necessary?

DR. CHATMAN: No, you said a good pelvic exam--

DR. BLANCO: Yes, what is a bad one? All right, I will retract that.

DR. CHATMAN: All pelvic exams are good exams.

DR. BLANCO: All right, I will go for that. All right, any other criteria? Anything else? Any other things that we need to look at? Should age make a difference?

Dosage of the hormones that they are on? Types of hormones?

No takers?
DR. CHATMAN: What about uterine size? I think the point Dr. Chatman made earlier is very, very important. This is a population, as opposed to the premenopausal where we haven’t seen a lot of perforations in the data, where we may see that. You have smaller uteri, thinner uteri, and that may be a problem. So, I think particular attention needs to be paid to that.

DR. ROY: With a more stenotic endocervix as well.

DR. CHATMAN: That is right.

DR. NEUMANN: I think this is also an issue when we get down to question number four, that the size and perfusion of the uterus is going to affect the particular technology that we use, and the dosage of heat or whatever it is that you are producing with this device that the patient receives.

DR. BLANCO: Yes, I think that is a very good point. Essentially, the prior studies done on premenopausal women with large, well vascularized uteri may not necessarily apply to the postmenopausal with the thinner less vascularized, less muscle type uterus in terms of amount of heat that is needed. So, some of the in vitro type of work probably needs to be repeated with postmenopausal uteri. Is that what you are saying, Michael?

DR. NEUMANN: Yes. I think we will get to it in more detail in number four.
DR. BLANCO: Okay. Anything else about history of successfully treated hyperplasia? Would those patients be included in a study?

DR. ROY: Donald, would you agree if it was simple hyperplasia it would be okay?

[Laughter]

DR. SHIRK: Yes, simple hyperplasia is fine. I still think the patient with adenoma and hyperplasia has something going on with their endometrium that is going to predispose her whether you treat her and then she responds and she is back to normal, and you take her off treatment, you know, should those patients be treated for the rest of their lives with progestins?

DR. BLANCO: I think other than simple, I would have a tendency to exclude those who have more complex, even though that will set the indications and the claim for the company but I think we are going to get into a problem there if we include those patients. There are not going to be that many that fit into that. Anything else on the hyperplasia? I think we beat that one pretty well yesterday.

DR. ROY: But all these factors are things that they are obviously going to have to report and keep track of.

DR. BLANCO: Right. We spoke a little bit about
risk for endometrial cancer already. Any other patient
classistics that you would deem important? No? Okay,
let’s move back to the tough one, 1(c). Does there need to
be some hormonal manipulation prior to inclusion into the
study?

I guess, you know, one way to look at this, and
that is why I was addressing what you said, Don, in terms of
the six times is, you know, we need to be somewhat realistic
in how do we want this to be used because that will be the
claim. So, if the study is set up that you need X number of
hormonal manipulations prior to offering endometrial
ablation, then that is how it will be set up. I think you
probably do need to make an adjustment but I certainly
wouldn’t want a lot of adjustments before being able to use
a modality.

I think Mr. Pollard would like to address the
panel.

MR. POLLARD: Yes, I just wanted to double check,
before we move back to 1(c), on 2(b). We kind of moved
right past the first four bullets and I just kind of wanted
to remind the panel that this is probably the kind of study
that is going to come back to the panel and you are going to
be looking at it, and are there no basic constraints you
want to place on a study of this sort with respect to age,
perimenopausal status, and actually the third and fourth
bullets may kind of roll into your discussion of question 1(c), but I just wanted to see. I mean, in terms of the kind of study that you would like to see at the end of the day, would you recommend some constraints in that regard?

DR. BLANCO: Anybody want to address those issues? I mean, is there an age parameter?

DR. SHIRK: It would be how many years postmenopausal. The only question might be if the patient is perimenopausal is she still having, you know, some hormone production that is causing her problems. But what do we define by menopause?

DR. CHATMAN: That may be the question right there. We should define menopause and say that the patient should have an FSH and estradiol and LH of certain levels to be defined as menopausal because age, obviously, is not the crucial issue here.

DR. BLANCO: Right.

DR. CHATMAN: And, both of those are the same question.

DR. BLANCO: And, the other issue that you are bringing up is that you don't really want perimenopausal. You want someone who is postmenopausal. For me, that was a given so I didn't even see why they put in the "peri."

Isn't that kind of what you are saying as well?

DR. SHARTS-HOPKO: But you might want to exclude
the marked outliers with an age of, I don't know, 40 or 45
to get out the 20s people.

DR. BLANCO: You mean like someone who has
premature menopause or something like that? Any comments on
that? Should there be a lower age limit if someone is well
documented to be postmenopausal?

DR. ROY: Well, if the reason they are not taking
their hormones is because of abnormal bleeding and they are
young, it seems to me they shouldn't be excluded because
they are probably more at risk for all of the deficiency
syndromes attendant with hypo-estrogenic status. So, I
wouldn't put any age limit on there, personally.

DR. BLANCO: Dr. Sharts, okay? Anyone else?

Okay, we have dealt with the younger. Is there a limit
above which you don't think it should be used? I would
think just the opposite. I mean, in some of the older women
this may actually be a better procedure than trying to do
some of the more interventional things that may end up
happening.

So, it doesn't sound like age is much of an issue
for the panel members, Mr. Pollard, and I think
perimenopausal, everyone is pretty clear, it needs to be
very firmly confirmed that the patient is postmenopausal.

DR. CHATMAN: And we should define it.

DR. BLANCO: Have at it.
DR. CHATMAN: Well, I don't know how to define that.

DR. BLANCO: Well, a period of amenorrhea, and do you want laboratory documentation? Do you want a period of amenorrhea--I don't know how else you would define it.

DR. CHATMAN: I think those are the parameters that we all use.

DR. BLANCO: Dr. Sharts, you look like you have a comment.

DR. SHARTS-HOPKO: Well, depending on what kind of hormone therapy they have been on and when they started. I mean, if they started in their 30s, they may not have a period of amenorrhea.

DR. BLANCO: Okay.

DR. ROY: We are not recommending, I don't think, doing studies only in people who are recently menopausal. Therefore, it would be suitable to do FSH or vaginal pH measurements, or different things like that, or serum estradiol values. So, I think they need to have a clear indication why the clinician and the patient believes that the patient is menopausal, and that should be recorded. But I don't know that it necessarily follows that we would require FSH above 20 or estradiol below 40 picograms, or vaginal pH above 4.5 because they are probably on some sort of therapy, and things like that, and they are having
problems with their therapy. So, I don't think we are necessarily recommending that they go off therapy to assure that they are menopausal.

DR. BLANCO: I think that is a very, very good point.

DR. CHATMAN: I think though since we are designing this study we need to have certain very clear-cut parameters. We need to start at the same base for every patient. Every patient should be clearly defined as menopausal, and I think the only way to do that is if somebody is on medication to take them off for a while, document that they are menopausal and then start the study, I would think.

MS. DOMECUS: I think patient enrollment in such a trial would be horrendous.

DR. BLANCO: Yes, I think it kind of defeats the purpose. I guess, at this point I would think probably leaving it general because, say, you have a fifty-seven year old who had a definite period of amenorrhea for three years before being put on replacement therapy, and maybe had an FSH back then that was markedly well elevated and well documented, to make that patient come off therapy now, you know, you will never get her in the study and you will probably never get her back in your office. So, I think it needs to be well thought out, and there needs to be some
certainty of the fact that they are postmenopausal, but maybe we will let FDA and the company wrestled with that one a little bit more. Is that all right? Can we move on?

All right, they want us to tackle the estrogen dosage and type of progesterone and dosage of estrogen. That, again, ties into 1(c). I am trying to get through these questions.

DR. ROY: Well, I think the practical issue here is how do you standardize that all the patients are at the same level of "responsivity" of their endometrial lining? If they are on estrogen alone and they have some sort of an endometrial echo complex assessment that suggests that there is some responsiveness, do you want to give them progestins and insist that the start of the therapy is after they have been so treated, or do they require a curettage so that they are all started with a certain endometrial lining or lack of lining? I think that is what we need to discuss. Does that matter when you go to ablation, like yesterday we were talking about maybe you don't need to give them GNRH analogs and to down-regulate them in order to use that system. Maybe you do. I mean, in this setting, what do you think?

DR. SHIRK: Well, in a preop work-up basically, I mean, anybody who is bleeding who is on just straight estrogen, I mean, I think they should have failed an estrogen-progesterone combination, not just straight
1  estrogen. I don’t think that is appropriate in today’s
2  world. But, you know, the question is basically whether or
3  not we should take these patients off their hormone
4  replacement therapy. Are you asking should we take these
5  patients off their hormone replacement therapy prior to
6  doing the procedure? If you are using a standard estrogen-
7  progesterone therapy they are already to the basalis. At
8  least on the combination therapy they are down to basalis.
9  It is like some of the studies using birth control pills.
10  So, I wouldn’t think that removing a patient from estrogen
11  replacement therapy—if that is what we are talking about--
12  prior to surgery is basically appropriate.
13
14  DR. BLANCO: Well, I think the issue is more if
15  you had someone who is totally on estrogen, and has not had
16  any progesterone, our position that prior to being enrolled
17  in the study the progesterone should be added and that may
18  solve the problem and they are no longer candidates for the
19  study. I think that is the issue they are looking at, and
20  should there be some requirements. You would put in a
21  requirement that people who have postmenopausal bleeding on
22  estrogen alone are not candidates at that point; they need
23  to be treated. They may need to be evaluated to see what
24  their bleeding is, but they need to be treated with
25  progesterone. So, patients who should be admitted to the

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having bleeding on that.

DR. ROY: Wouldn't that be the point? I mean, the only reason I would think anybody would go to straight estrogen in today's world is if somebody is bleeding on an estrogen-progesterone combination. Okay? I mean, putting somebody on straight estrogen is making them equivalent to their fat sister. I mean, basically you are running estrogen levels up really high. So, I mean, that would be a total exclusion, as far as I am concerned. I mean, they need to have failed on estrogen-progesterone; conventional estrogen-progesterone therapies.

Just to argue the other side, there are a lot of women, or at least a lot of my colleagues feel that their patients are so refractory to the medroxyprogesterone acetate being added, and become so symptomatic with its addition that they will do anything, and are doing various strategies of estrogen alone therapy, including lower doses than we are customarily using, and Monday through Friday, or three times a week, all kinds of different things in order to not employ progestin therapy.

DR. BLANCO: It doesn't sound like there is a lot of consensus on this particular issue.

DR. ROY: I think it comes down to if you are going to have the cohort of patients who are willing to consider going on any of these studies, the companies may
have to pay just to enroll many more patients because of all of these little caveats and differences in doses, and things like that, because if we insist that everybody fit into a specific slot it is, first of all, going to be difficult to do and, second of all, what are you going to extrapolate it to? So, I think the price that is going to have to be paid is studies that are of a much larger size.

DR. BLANCO: But if you did the saline infusion and you did a polyp, you wouldn't make that patient a candidate for the study. You are talking in terms of hormone replacement that they are on, you have to be kind of broad on that because there are just so many variations of it.

DR. ROY: Yes, so they have the bleeding. You run through these different diagnostic steps. They don't fall out because of that, and then it is an issue of do the patient and physician want to keep manipulating things, or have they deemed it sufficient, whatever they have done? I guess the FDA's point, and a very legitimate point is that if you allow those differences to occur, gaining entry onto the study, will the outcome be worth looking at? I mean, if you have just estrogen alone people versus estrogen and progestin, different combinations, permutations—it is not an easy answer.

DR. SHIRK: I think we have got some standard
answers over the long haul as to what the risk of developing endometrial cancer is in patients on estrogen-progesterone therapy. I don’t think we have good answers on the alternative group of using estrogen alone.

So, one of the questions, as Dr. Chatman brought up, was basically that we have to not only ask is this effective but, more importantly, we are asking is it safe, and one of the major safety issues is the incidence and also the detection of endometrial cancer in the future.

I would agree with you that there are a lot of women that have a lot of problems, especially on synthetic progestins, and the next question would be with the new micronized progestins coming on the market is that going to become less of a problem? Then the question down the line is what is our endpoint in the study? Maybe you have a better answer for patients on straight estrogen replacement therapy, followed over time, as to what their risk factors are, and how are you going to biopsy these patients? I mean, obviously, you don’t have to biopsy patients on a yearly basis who are on estrogen-progesterone, but you do have to biopsy patients who are on estrogen.

DR. BLANCO: Well, let’s take a step back because I think the issue we are trying to discuss is should we have a uniform hormonal therapy given to patients prior to inclusion into the study? Okay? In order to say that that
is important, we have to say the outcomes may be different if you don't set the study up that way. The complication of that is that, therefore, the indication is going to be that you have to go through that process each and every time. So, is there enough difference between individual types of estrogen and progesterone where you might think the outcome might be different, or is it just estrogen alone versus estrogen-progesterone combinations, and should they be differentiated? Or, should one of the two be excluded from the study? I think that is the question.

DR. CHATMAN: Have we covered this by suggesting or requiring that patients have medical manipulation of their hormone replacement therapy before they enter into the study?

DR. BLANCO: That is part of the question. I mean, that is part of the issue. I mean, should patients on estrogen alone be candidates for the study with no further manipulation? Do you require that they be put on estrogen-progesterone and then, if you require that manipulation, if someone is on estrogen-progesterone that might be a candidate do you require a change to a different estrogen-progesterone before inclusion? I think that is the question. I think we can go into individual types of estrogen-progesterone and we will never get done.

DR. CHATMAN: Yes, we would be all day trying to
do that.

DR. BLANCO: Right.

DR. ROY: But I think in a way we have sort of set the wire, or set the bar because haven't we said that they have to have jumped through the hoop of no endometrial echo complex exceeding a certain amount? So, whether you are giving estrogen alone, as some of my colleagues are doing at lower doses and varying schedules, or whether you are giving estrogen-progestin at least the end organ is more or less below a certain amount.

DR. CHATMAN: That seems reasonable.

DR. BLANCO: Would that get us around the issue -- that would mean you could be included in the study whether you are on an estrogen alone or an estrogen-progesterone combination as long as on your saline infusion ultrasound your endometrium is below X mm and so forth. That seems to be a consensus now.

Going back to 1(c), should there be a change? Should you try a hormonal change first before proceeding on the pathway to possible endometrial ablation?

DR. ROY: Well, my sense would be--I just hate to interfere with physicians' and patients' management decisions. I mean, if they think they have gone as far as they are going to go and this is a legitimate alternative, then I think we should leave it up to them. If they want to
manipulate for a further period of time, then let them. But
I think what is necessary is that all these steps be
captured so that they can be looked at to see if it makes a
difference ultimately.

DR. SHIRK: My suggestion might be to go back to
the original studies with the premenopausal women.
Basically, one of the criteria was failed hormone therapy.
So, why don’t we just put that as a criterion, just failed
hormone therapy, and that is pretty non-specific without
using any specific guideline?

DR. BLANCO: So, if they brought in a study two
years from now that essentially took all-comers as long as
their ultrasound thickness of the endometrium was below X,
whatever is decided, but some had been on estrogen alone,
some had been on estrogen-progesterone, some had been
changed two or three times, some had never been changed from
one regimen, that would be acceptable? Because that is the
question. I mean, that is the guidance we want to give. I
don’t want to leave it fuzzy because, you know, they need
some clear guidance. Do we think that one or more
manipulations or changes in the hormone is required? You
are going to make a smaller subset because some people are
going to respond to the change in hormones. To some extent,
what we are asking is, is endometrial ablation a benign
enough procedure that you would rather do that than a change
in hormones, to some extent? So.

DR. CHATMAN: It sounds conflicting to me because what he said was failed hormone therapy. If I have a patient who is on hormone replacement and she bleeds, that is failed. I don’t have to do any manipulation in order to get into the study if we use that terminology. We have to say that there has to be some change, some attempt at a different formula of some kind or another.

DR. BLANCO: But, you see, that is the point I am trying to get at. The point I am trying to get at is if you make it that general, you know, you are basically leaving it up to the physician to decide when it is failed hormone therapy. That could be, you know, after three months of estrogen alone; it could be after two years of four different estrogen-progesterone combinations or estrogen alone combinations or progesterone alone. So, that is why I am trying to get a little bit more focus on that issue.

Going back again, do we require change; do we leave it general? And, are we going to accept the inclusion criteria of being that general when a study is done that way?

DR. ROY: I think it is real life and for some people one therapy may be all that the patient will accept or tolerate, or the physician wishes to undertake, where for someone else they will do everything possible to avoid any
sort of surgical manipulation, and they will go through five or six different groups. I think the key point is that the uniformity that we require to assess the suitability of acceptability of study results I think we have if we insist on a certain endometrial echo complex thickness, or below a certain amount regardless of whether it is one manipulation or five manipulations.

DR. BLANCO: All right. Any other comments on 1(c) or any part of 2?

[No response]

Let's move on to three. It is almost ten o'clock and we are supposed to take a break. Do you want to go ahead and take a break and come back and tackle three and four after the break? I see some heads nodding yes.

DR. CHATMAN: Did we address uterine size? Did we settle on that?

DR. BLANCO: I don't think we mentioned a particular size. I think we said we are concerned about size and higher rate of perforations because of the thinner, smaller uterus. But let's talk about size.

DR. CHATMAN: What about on the other end that would imply that there is organic pathology that is causing bleeding.

DR. BLANCO: Yes, and I think also this procedure may not be that--I mean, there is a certain amount of size
that occupies the endometrium so it may not be all that useful.

DR. SHIRK: The other question is that some of these devices have specific lengths, and if you have a uterine size below a certain length you are going to have part of the device really out in the endocervical canal, and are we creating problems of treating the endocervix as well as the endometrial cavity?

DR. BLANCO: So, how about a statement to the effect that the size of the uterine cavity needs to be within a size that is compatible with the particular product being tried, and leave it general rather than saying size because industry may come up with postmenopausal handle and a premenopausal handle that has a different size. So, some attention needs to be paid—I mean, they may not, but some attention needs to be paid to make sure that the uterus is not below a certain size and, therefore, the bag or whatever the technique, the burning surface or the treatment surface, to make it more general, the treatment surface would be inside the endometrial cavity and, at the same time, it can't be large enough that the treatment surface would be insufficient to treat the entire endometrium.

DR. ROY: Or, conversely, not big enough. You know, some may, for reasons of pathology, be too large.

DR. BLANCO: Right.
DR. ROY: I wouldn't want endometrial ablation under that circumstance.

DR. BLANCO: I think there is probably some upper limit beyond which you don't really want to do this.

DR. CHATMAN: There are some size parameters already developed.

DR. BLANCO: That is why I didn't mention numbers.

DR. CHATMAN: But they use numbers.

DR. BLANCO: Our suggestion or our recommendation is that there be some numbers that are applicable to the particular instrument being used in terms of size, not too large, not too small. But that is going to depend to some extent on the individual product. Right?

Let's go ahead and let's take a break before we finish number three and four. Let's take a 15-minute break, so if we could be back and reconvene promptly at 10:15.

Thank you.

[Brief recess]

DR. BLANCO: Let's come back to order. I think there are a couple of comments that needed to be made, and then we will go on to three and four. I think we are ready to start. Miss Young?

MS. YOUNG: Yes, I would just like to bring up a couple of things specifically with regard to age and the other with regard to cosmetics.
I think that the postmenopausal woman actually falls within a very broad age range, and I think that it would be very difficult really to sort of give that age as sort of a beginning and an end. So, I really think that it is an individual matter that needs to be considered here. The patient's viewpoint in terms of how does this bleeding affect her life; how important is it to her. That is something that she needs to talk to her doctor about and the doctor needs to understand that there may be some psychological issues here and this, you know, brings up the matter that Dr. Shirk raised, which had to do with, you know, should this just be a cosmetic procedure. For some women it may be psychologically extremely important that a certain amount of bleeding is something beyond which she will not tolerate. Another woman might be able to tolerate a great deal more bleeding. So, I think it is something that has to be worked out with the physician, and those things need to be taken into consideration.

DR. BLANCO: Thank you. Dr. Roy?

DR. ROY: I think the other thing I don't believe the committee was saying needs to be clarified, and that is that when hormone replacement therapy is instituted, just like with birth control pills or in the postmenopause, there is an adjustment period, and the vast majority of atypicality to bleeding tends to go away with use. We are
not recommending that at the very outset, if you have some spotting or heavy bleeding, that you immediately capitulate. I think it would be unlikely for clinicians or patients to just say that the majority would not fit into that categorically. I think what we are suggesting is that when there is a persistent problem that has been manipulated and has failed, and they go through the assessments and come out the other end with an endometrial echo complex that is below 5, or whatever, that is the cohort that would be candidates for this study.

DR. BLANCO: All right. Let’s move on to three and four. Three is, what should the primary study endpoints be, i.e., reduction in bleeding versus amenorrhea. The (b) part of three is what role should secondary endpoints, quality of life indicators, play in clinical study design for postmenopausal endometrial ablation? Anybody want to tackle that one?

DR. CHATMAN: Well, we can’t have as an endpoint amenorrhea.

DR. BLANCO: We can or we cannot?

DR. CHATMAN: We cannot. I don’t think that is practical.

DR. BLANCO: Okay, someone says why couldn’t we have that? I am sorry, Dr. Katz, go ahead.

DR. KATZ: I was just wondering how the answer to
this question relates to the questions we were discussing yesterday for premenopausal women, where we have these two different types of endpoints. Is there anything different about postmenopausal women in this regard? We certainly have that as a frame of reference.

DR. SHIRK: I certainly think the studies that have been done in this group of women show that there is a much higher rate of amenorrhea. That is obviously not 100 percent amenorrhea. That is a goal but I don't think it is a reasonable goal with any technology.

DR. BLANCO: So, what should the study endpoint be? I mean, should it be a decrease in the bleeding? You said not amenorrhea, and why not amenorrhea? Just because you don't think it is going to happen? Is that sort of what you are saying?

DR. SHIRK: So, what are you going to compare it to, hysterectomy as a control model which is 100 percent amenorrhea?

DR. ROY: Well, obviously the result of ablation will in part be amenorrhea, a certain proportion will, and the other proportion will have reduced bleeding. So, these are two legitimate factors to measure and to track over time. But you are absolutely right, what is the control group?

DR. CHATMAN: Well, the control group is
menopausal women who are not on hormone replacement therapy.

DR. ROY: So, it is legitimate to compare what is going on with them, or is it menopausal women who are on hormone replacement therapy, or who continue to try to be on hormone replacement therapy even though they have had problems with it? I think that is the more appropriate control group, not the ones who are not on hormone replacement therapy.

DR. KATZ: It might be hard to do a randomized study--

MS. YOUNG: Exactly. Who wants to be randomized off? Yes.

DR. ROY: But if you think about it, both are on hormone therapy, one has had ablation and one has not. How much amenorrhea, how much spotting or bleeding do you have?

DR. NEUMANN: I think we are talking about a study endpoint here as opposed to any specific therapeutic outcome, and it seems to me that the outcome measure that we are looking at is the degree of bleeding, and as an outcome measure it should be that, and that includes amenorrhea as well as anything else.

DR. BLANCO: Any other comments?

[No response]

All right, what about secondary endpoints?

Quality of life indicators? Mr. Pollard?
MR. POLLARD: Thank you, Dr. Blanco. I just wanted to get a little further clarification of question 3(a), and as I understand it, the panel recommended that the endpoint be reduction of bleeding, the degree of reduction of bleeding. I guess the sort of follow-up question that maybe should have been written in there is when we will be looking at proposed study designs they will come to us-- manufacturers will come to us proposing that endpoint but it will really be constructed in the context of the control group and some percent, either bringing that bleeding below a certain point or, you know, the patient serving as their own control and reducing a certain percent. Could the panel comment on essentially what constitutes success using this endpoint?

DR. BLANCO: Success is having a patient continue their therapy.

MR. POLLARD: The hormonal therapy, you mean?

DR. BLANCO: Yes, with whatever the reduction in number of days of bleeding because if it takes it from an unacceptable range, which is why she went on the study in the first place, to an acceptable range, then I think that is success. I think for the vast majority, they would prefer amenorrhea, as was alluded to yesterday, even with higher temperatures for longer durations as a maximum therapeutic range beyond which you can't go, which doesn't
assure amenorrhea.

MS. DOMECUS: Although if we use staying on hormone replacement therapy as a definition of success, there could be other reasons why patients discontinue even though their bleeding is treated sufficiently.

DR. SHIRK: I think most of the studies that have been done have shown that there is about an 85 percent amenorrhea rate in this group of patients, which obviously then plugs it back into using a control group of conventional endometrial ablation means versus the device. Again, do we want to go back to the standards that we were using before using hysteroscopic endometrial ablation or Rollerball? You know, conventional means of endometrial ablation versus, you know, the device as a control group.

DR. BLANCO: Well, I think maybe what you are bringing up is that the control group plays a role because one control group would certainly be to use Rollerball or resection, but could you possibly use another control group here, which is, you know, continual hormonal manipulation? I mean, another possible control group might be that you start changing the hormones to something else.

DR. SHIRK: Then the question is you have to decide what your endpoint is going to be to decide what your control group is going to be, and, you know, is discontinuation more of a subjective finding than--what
objective endpoint can we find that will allow both a
control group and a research group?

MS. YOUNG: Well, from a woman's standpoint
reduction in bleeding, hopefully complete stopping of
bleeding, would be her endpoint that she would want to see.
But if we accept that reduction in bleeding has to be the
primary endpoint, why can't she serve as her own control?
Why do you have to have another group doing the Rollerball
or something or other else?

DR. BLANCO: Deadly silence! Anybody want to
answer that?

DR. SHIRK: The only problem there is that I don't
think any of us know enough about what the endpoint should
be, what the optimum endpoint should be to establish a
number to say 85 percent of patients with amenorrhea, 75
percent, 50 percent--I don't know what an optimum or
realistic number would be. I mean, I have a guess but I
don't think there are enough studies out there that would
basically allow you to use that as a stated endpoint with no
control group.

DR. BLANCO: Well, what would be the alternative
in today's practice? What would be the alternative to
ablation? I mean, what happens now if a woman comes in and
she has postmenopausal bleeding. She gets evaluated; she
doesn't have polyps; she doesn't have submucosal myoma; she
doesn't have endometrial carcinoma or any hyperplasia. I mean, what is the comparable option that she is likely to receive at that point? I mean, I think it is hormone change, change in the hormones. So, do people go into resection? Is that the other option? You mentioned surgery, Dr. Roy. Do you want to elaborate?

DR. ROY: Well, I think either local surgery like endometrial ablation or else hysterectomy, but I don't think the bleeding, as was alluded to before, is appropriate to compare to the hysterectomy group. I think it is more reasonable to compare it, if you could get a group to continue the hormone manipulations, etc., and didn't go to some sort of endometrial ablation, or went to a different, more traditional endometrial ablation approach.

DR. BLANCO: All right, and when will the patient and her physician feel like they have accomplished what they wanted, which is again a roundabout way of asking the endpoint? To me, it seems amenorrhea and amount of bleeding are the key issues. I would agree that coming off hormones has too many other confounding variables that would play on it to use that. So, I think we are back to amenorrhea, the rate of amenorrhea and the amount of reduction in bleeding and, to some extent, not as a primary but I think quality of life as I think Miss Young said. You know, did bleeding go down enough that she is comfortable
with it and, you know, is comfortable with that amount? Any
comments?

DR. ROY: I don't see any problem with having the
patient be her own control.

DR. BLANCO: Well, how are you going to have her
be her own control? I am a little lost on that.

DR. ROY: Well, you know that she had bleeding,
and now she either has a cessation of bleeding or she has
substantially less bleeding, or possibly more bleeding.
But, at least you know what has happened to her "bleeding
pattern" and you know, by querying her, whether she is happy
with that and she is willing to tolerate it, willing to
continue her therapy or if she is going to stop.

DR. BLANCO: But the issue then becomes what is an
acceptable level of women who either become amenorrheic or
say their bleeding has decreased that you would say this is
part of the armamentarium that should be used on these
patients. Are you going to require 80 percent, 50 percent,
20 percent?

DR. ROY: No, you compare it to the group who
don't want to go on to a local therapeutic modality such as
this who discontinue therapy. I mean, that would be one way
to look at it.

DR. BLANCO: I am not sure I follow you. I think
the control group would be women where you would need to
alter or manipulate the hormone treatment and then compare them because what is going to happen, okay, I have someone on estrogen-progesterone combination X at Y dose, and what I am going to do now is if she complains of bleeding, I am going to make sure she doesn't have hyperplasia, by whatever methods I want to do that, and then I am likely to change her to this other dose. Then I am going to treat her for X length of time, and at that point I am going to see is she amenorrheic; did I decease the bleeding; you know, is she happy or at least accepting of the amount of bleeding? To me, it would seem that is what you would want to compare. I will stop there.

DR. ROY: You know, the issue here is one of efficacy. Obviously, the question is what point of efficacy do we want this thing set at, what bar? I think at this point we are all agreeing that the patient's desire in this thing or the only endpoint is amenorrhea. Maybe diminishing bleeding is one thing. Probably the more important issue with this device and this study is going to be safety. So, probably the issue here is basically just setting some percentage of efficacy that the panel or the FDA feels is a guideline, and I don't know whether we use existing data or whether we just say, you know, 75 percent of patients should achieve amenorrhea.

MS. DOMECUS: It seems to be difficult to set a
precise number, and maybe we can go back to Dr. Roy's
suggestion about the patients remaining on hormone
replacement therapy as a definition of success but then add
into that all patients who discontinued but didn't do so for
reasons related to their bleeding, and then I think the
patient could serve as their own control if that was the
definition of success.

DR. BLANCO: Well, I am troubled
will tell you what I am troubled by. That makes the
assumption that this procedure has an extremely high safety
rate. Okay? Because what you are basically saying is,
well, it is okay to use this procedure as just one of the
other parts of the armamentarium whereas, if we have a group
that receives ablation and a group that receives hormonal
therapy, and the hormonal therapy gives me as good an
amenorrhea rate when I make a change, or a decrease in
bleeding as the endometrial ablation, and I have a one
percent or whatever percent rate of perforation or
complications--I mean, if we think the inability to do the
procedure is high in the premenopausal, think about the ones
with cervical stenosis, small uterus, higher risk patient to
whatever anesthesia they are going to be given. You know, I
think if we don't compare it to something like hormonal
manipulation and say, oh yes, the outcome is a lot better
then why in the world are we going to put these people at
risk, older people at risk for the anesthesia, the possibility of a failed procedure or whatever complications come from the procedure, when all we have to do is change their hormones and we would have done the same thing? So, I am real leery of using the patient as her own control. I think we have to have another control, and this procedure has to be better than just changing her hormones and, therefore, it is worth taking the risk of the anesthesia and the possible failed procedure and the possible complication rate.

DR. SHARTS-HOPKO: But one of the problems with interventions around menopause issues is that menopause is all about quality of life, and it is all from the woman's perspective, what quality of life of life is and how to enhance it. I mean, we aren't going to know for many, many years whether continued hormone replacement therapy did anything for her life span since it has all been manipulated so much in the last couple of decades. I mean, we are 30 years from knowing anyhow probably.

DR. BLANCO: Yes, but would that be any better if they got ablated? Does that make any difference in her quality of life?

DR. SHARTS-HOPKO: Well, that is what Diony said.

MS. YOUNG: Let's be realistic about this. Let's say the studies are done; the device is used in
postmenopausal women. The device has been approved for
premenopausal women. The word is going to get out. I can
tell you, I think in the real world you are going to have a
real problem getting the control group, the sort of control
group that you want that isn’t going to have this by the
time we are starting to study this because I think that
women are going to know that this is a device that has been
found to be efficacy and safe with premenopausal women.

Great. If it works for them, why can’t I have it? No, I
don’t want to be randomized out of this study so that, you
know, some women get this and I don’t get it because, you
know, I want my bleeding to stop and this has been shown to
work with premenopausal women, well, I want it too.

DR. BLANCO: I guess my answer to that would be
maybe you could do a crossover after a certain amount of
hormone manipulation. If they failed that, then they could
go into the endometrial ablation arm.

I am just concerned about being a little cavalier
in terms of the use of this device in these women where we
have identified a significant set of concerns that are over
and above the premenopausal woman, essentially basically
saying, well, we are just going to use it and then we are
going to figure out what our perforation rate is and what
our complication rate is without really being able to say,
hey, you know, we could have stopped your bleeding just as
well by having done this with hormones and not put you through these risks unnecessarily. That is my concern and why I definitely would use a control group that would be some medical manipulation and arrive at the data that way. You know, if you could do it where you could do then a crossover, say, after three months or X number of months of medical manipulation and you still were having problems, then you would drop into the other arm of the study and go from there. Somewhat of a crossover; you wouldn't crossover to the other group.

DR. ROY: My problem with your logic is that I wouldn't entertain the use of this product until after the medical manipulations had failed.

DR. BLANCO: Okay.

DR. ROY: So, I disagree with you that it is a suitable alternate group to use as controls.

DR. BLANCO: But we didn't recommend that. You did make the statement when we came back to the meeting that this shouldn't be used sort of very promptly after hormonal therapy but we really didn't make that statement that you just made, that you really want medical manipulation prior to their being able to enroll, and failure of medical manipulation prior to their being enrolled. So, we are changing a little bit our answer to number 1(c) there from what we said before.
DR. CHATMAN: I thought it was one of our requirements for patients to undergo ablation.

DR. BLANCO: Maybe I misunderstood that.

DR. SHIRK: Do we want to just go back to our original study design where we were comparing basically hysteroscopic endometrial ablation versus the device ablation as a control?

DR. ROY: I think that is the only legitimate way to do it because then you have all of the other parameters that you can directly examine—the issues of difficulty in cervical dilatation, perforation, amenorrhea rates, reduction in bleeding rates—because both groups will be getting hormonal therapy. Therefore, the issues about quality of life and things like that could specifically focus on the impact that the amenorrhea rate and/or the bleeding reduction rate has on quality of life over and beyond that which you would expect to be improved with estrogen or hormonal therapy.

MS. DOMECUS: But is hysteroscopic Rollerball ablation even approved for postmenopausal women right now? I mean, can that be used as the gold standard for the control group if that is not even approved for that in the first place?

DR. BLANCO: I can't answer that question. I don't know if anybody can. Dr. Chatman?
DR. CHATMAN: That was my question. I mean, you know, do we have data on the postmenopausal women with the hysteroscopic resection? We don't have enough.

DR. BLANCO: That is the point, that is why I was trying to look at a different control because I don't think that--you know, maybe it is a bias that they go to hysterectomy or some more radical procedure than the resection but I just don't know that there are that many that get resected.

MS. DOMECUS: And then if you prove that they are equivalent to that, what have you really proven if that hasn't been established in the first place? I still think the patients should serve as their own controls.

DR. SHIRK: I don't know what kind of approval the electrical devices have for endometrial ablation, how open-ended it is with the FDA.

DR. HARVEY: They have been going through a 510(k) and they don't have the same--

DR. SHIRK: The resection?

DR. HARVEY: The resection and Rollerball instruments. So, they don't go through the same sorts of clinical studies to establish safety and efficacy.

DR. SHIRK: I understand. So they are open-ended enough to say that it is FDA approved for that procedure if the physician wishes to use it that way.
MS. DOMECUS: But is it the gold standard? Even if the FDA approval wouldn't limit its use in postmenopausal, is it the gold standard enough to constitute a control group?

DR. SHIRK: I don't know. A lot of it is being done.

DR. KATZ: What is the labeling for these devices?

DR. BLANCO: You mean for the Rollerball?

DR. KATZ: Yes. What is the labeling? Does it mention postmenopausal conditions?

DR. HARVEY: Colin, would you like to comment on that, or Dr. Yin?

DR. YIN: I don't think so because that is a pre-amendment product and usually the claim is such a wide range.

MR. POLLARD: Actually, it is not pre-amendments. The hysteroscopic resection came into use in the early mid-80s, but the data that it was based on was premenopausal women. I don't know precisely the labeling restrictions. I actually think it is silent with respect to the postmenopausal situation. Whether or not people consider it to be an alternative or a gold standard, I actually think it is probably--well, just to be to the point, the labeling is silent as far as I know.

DR. BLANCO: Well, I think the panel has given the
FDA a flavor for the variety and controversy within question
three, and I think we probably have given them all the
controversy and variety--go ahead, and we will move on after
some comments there.

DR. SHARTS-HOPKO: I want to comment on 3(b),
quality of life indicators. I think for that specific
question--this relates to a comment that I made to the
Chairman during the break so I will say it now for the
record. One of the things we don't know fully is what our
uterus does for us in the latter half of our life. But in
the last 30 years we have sort of come to believe that it
does some stuff, whatever it is.

So, we certainly don't know what an ablated uterus
does for us in the second half of our life compared to an
unablated uterus or no uterus. So, I think that for quality
of life kinds of comparisons there are plenty of studies out
there, plenty of quality of life surveys that are
administered to women comparing those who have had a
hysterectomy with those who haven't, and I would like to see
those kinds of comparisons made, ablated, non-ablated and
hysterectomy groups.

DR. BLANCO: Yes, I think that is very important.
Also there are issues of what does an ablation do in terms
of ability to sample the endometrium if there is later the
development of endometrial hyperplasia or carcinoma? Does
it alter the prevalence of the possibility of that
development? I think there are a lot of issues. So, I
think the recommendation there would be that post-market
analyses need to be done to make sure what the follow-up is,
what happens to these women who are ablated and to their
uteri as years pass from their ablation.

Any other comments on number three?

DR. ROY: Could I just make a plea that we try to
refine the tools to assess quality of life so that we can
possibly differentiate what impact the ablation procedure,
as it pertains to increasing amenorrhea or reduction of
bleeding, has on the quality of life over and beyond, or in
separation from the hormone replacement therapy benefits
that may accrue.

DR. BLANCO: All right. Let's move on to number
four. I think there will be some information on this. Do
specific device design considerations or thermal modalities
require feasibility studies for the postmenopausal
application? Dr. Neumann, I think you want to make some
comments here?

DR. NEUMANN: I think we are dealing with a
different situation here in terms of the postmenopausal
uterus compared to the premenopausal uterus and, as such, I
think it is important that studies be done to demonstrate
the effectiveness of the device in terms of actually
creating the ablation.

I would like to propose several approaches to be considered. One of the things that I noticed in the approaches with some of the devices that have been previously examined is that most of the approaches have been really empirical, taking a fresh uterus from hysterectomy and doing some studies, and then sectioning it and looking at the areas of damage and necrosis.

It seems to me, and perhaps Dr. Katz can comment on this since it is more in his field than mine, that there are biomechanical models that look into the effect of tissue thermal properties and perfusion in terms of temperature distributions and heat flow. I think that is going to be much more critical to look at this where one has a greater amount of variation in the anatomy and in the physiological function.

I think also that the mode of creating the ablation is going to be more critical here. Whether one uses heat and whether one applies the heat by means of hot water, electrical discharge, RF heating, or whether one uses other approaches such as the optimal approach which may, in fact, be heat, the so-called 360 degree laser, I think all of these factors are important, plus the distribution of the source. Perhaps, as we discussed yesterday, multiple electrodes are a good way to get uniform distribution of
heat in the premenopausal uterus. But do the variations that come from areas over an electrode as opposed to areas between an electrode, are these sufficiently great in the thinner myometrium that, in fact, this is cause for concern? I think all of these kinds of studies would be done in vitro before one actually goes to a clinical study.

DR. BLANCO: Any comments? I guess the other thing with that would be two items that I would like to bring up. One is that I think here, like Dr. Roy suggested in terms of standardizing endometrial size so that we are comparing apples and apples and end organ effect, I think we probably need to have some measure of myometrial thickness because some postmenopausal women, especially if they are put on the study, you know, three years after they went postmenopausal, may have a lot thicker myometriums, maybe more comparable to the premenopausal where someone put in 10 or 15 years after her menopause and may have a very thin myometrium. So, I think one of the things that needs to be addressed in the in vitro model for the preclinical studies would be myometrial thickness and its effect on heat dissipation and what it does.

But I think also in the clinical study you may want to look at myometrial thickness and have some parameters of myometrial thickness inclusion or exclusion criteria, depending on what information is found in the
preclinical studies about myometrial thickness and the
effect of the particular device on heat dissipation and so
forth.

I think the other issue that I would like to see
from some of these studies--I still am very concerned about
perforation and I think that is going to be even more
important in the postmenopausal women than the premenopausal
women, and I think that some preclinical models need to be
developed as to what does this product do whenever you have
a perforation, and to actually create partial as well as
complete perforations and see does the machine actually shut
itself off. Is that a fail-safe mechanism so that we are
not, you know, endangering bowel or any other pelvic organ?
What does the machine do when you have that type of setting,
and to do that in a preclinical type study to have an
understanding of it.

DR. KATZ: I have several comments, sort of
deriving from what Dr. Neumann said. I think we can agree
that this is an area of medicine where there really isn't
the scientific understanding of the system that we would
like to have to design instruments that intervene in it,
especially when we talk about the menopausal uterus but, in
fact, generally speaking even the premenopausal reproductive
tract. There is lots of knowledge of some of the issues
that Dr. Neumann mentioned about the structure of the uterus
and how it impacts the effects of any particular ablation instrument. We just don’t have that knowledge.

On the one hand, it would be helpful, beneficial to our charge if that knowledge were forthcoming, but that is not FDA’s purview; that is NIA’s and NICHD’s purview to try to promote research through RFAs to stimulate more research in this area. There isn’t very much.

Now, given that, what can we do? There are in vitro approaches. I just thought I would give you some of my views on in vitro versus in vivo approaches to design and evaluation of instruments for this in the postmenopausal uterus. That differs in the premenopausal uterus. Working with tissue, dead tissue in vitro to begin with is useful. It ignores the effect of the vasculature in removing heat and, so there is a fundamental thermal difference in anything that you do in that system unless there is some clever way that you can build an in vitro system that reproduces that, and maybe that is possible. It might even exist; I am not aware that it does.

We heard yesterday about studies where women undergoing elective hysterectomy volunteered to have an ablation procedure immediately prior to hysterectomy and I think one can learn something from that. Probably that is a very crucial type of study that one could do to ask questions about the suitability of different instruments. I
I think that is really a critical type of study design that one would have to do.

I guess one question that Dr. Shirk and I were talking about is are there any animal models that have any relevance to this question, and I don't know the answer to that. I mean, I know from other issues in the reproductive tract, especially when it comes to the organs in the reproductive tract there are answers seldom, at best, and I don't know that there are. So, this is very tough.

When it comes to device design, in the absence--I mean, it is hard for me to think of a really definitive type of study other than volunteering to have types of different procedures done prior to elective hysterectomy.

DR. BLANCO: Any other comments?

DR. SHIRK: I think, you know, the issues are obviously design. The two effects that concern me the most are basically the change in radiator effect and the uterus itself so that the postmenopausal uterus obviously has significant reduction in blood flow and essentially the ability to carry heat away from the tissues. I don't think anybody is able to quantitate that, and how this varies with different hormone regimens. Okay? So, we not only have the postmenopausal women who has no hormone therapy on board, but now a woman who does have hormone therapy on board and how does this vary, and what does this do to the thermal
penetration?

The other question is basically one of simply elasticity. That can be extremely variable in patients. Obviously, you can simply rupture a uterus by over-dilating the uterus, just by extending the uterine cavity, and that is a high rupture. So, the uterine cavity is not really distendable in a lot of postmenopausal patients on or off hormone replacement therapy, and how would one design an instrument that basically accommodates to the differences in loss of elasticity of the organ?

MS. YOUNG: I was going to ask following on what Dr. Katz said, and I was sort of going to ask does the panel know what studies actually have been done on postmenopausal uteri after a hysterectomy, specifically to look at the changes that there are? I mean, in a postmenopausal uterus that has been taken out of a woman, can you then measure things such as elasticity, or not? Obviously, you can measure thickness, but what studies have actually been done on old uteri?

I mean, looking at this sort of realistically, the majority of them are discarded. I just wonder if there are studies, physiological studies that have been done, taking a bunch of these uteri and measuring--using physiologic, chemical, all sorts of different parameters to measure what is left now in the old uteri in comparison with the new
uteri that have been taken out of premenopausal women? I don’t know if you understand what I am sort of trying to get at but have we got this information?

DR. SHIRK: The answer is who cared?

MS. YOUNG: Who did care?

DR. SHIRK: Right. Why would you care until we got into something like this?

MS. YOUNG: Okay. We are caring now. Right?

DR. KATZ: But there are lots available. In other words, if one wanted to do pressure volume studies, you could get at elasticity that way. Right, Mike? I mean, the technology exists. So, in terms or recruiting people there is certainly an abundance of potential volunteers, but I don’t think there is very much data on that. Mike, do you?

DR. NEUMANN: I am not aware of any.

DR. BLANCO: I think the panel is calling for some basic science work on this issue that this particular technology has brought forth. We are venturing forth on the technology without having as much of the basic science knowledge as we probably need.

DR. KATZ: Well, let’s work with that a moment. The same questions apply to the premenopausal uterus. We are talking about safety issues here. As much by empiricism as anything else, we believe the data suggests that these instruments are relatively safe in the premenopausal uterus.
but that wasn’t the result of any fundamental mechanistic understanding of the properties of these instruments and the mode of insertion. It was just sort of work done empirically.

This is new territory now when it comes to an organ that may be more susceptible to injury by application of an instrument. So, it is not just the obtaining of these basic data on properties of the uterus that will affect the design of these instruments, it is the redesign of the instruments to accommodate. I mean, this would be a more challenging bioengineering problem for the manufacturers to determine the suitability of current instruments.

DR. CHATMAN: You can make it very, very complicated because atrophy is not a static process. If it is atrophic at 52, it is a lot more atrophic at 82.

DR. KATZ: Yes.

DR. CHATMAN: It is a certain size at 51 and it is a different size at 82. So you could actually divide age groups, 50-60, 60-70, or whatever. You could make it extremely complicated if you wanted to. I mean, you have a body of postmenopausal uteri that go from 50 to 100, and this could get extremely complex, if you wanted it to be, study.

DR. BLANCO: I think that brings up the issue of myometrial thickness, probably the sounding depth of the
uterus. All that data needs to be obtained because that will give you some idea of how to stratify the data that you get in terms of what you are saying about the smaller uterus as the woman ages, which is probably more important than the age per safety and efficacy.

DR. KATZ: I just wanted to give an opinion, and that is that while temporally that further complicates the problem, I think it is a problem that can be satisfactorily addressed. I don’t think that this is such a big sort of engineering challenge or scientific challenge that it could not be satisfactorily addressed. I just think--Mike?

DR. NEUMANN: I didn’t mean to interrupt. I certainly agree with you that the problem can be addressed. I am a little concerned that maybe there is some feeling in the audience of the manufacturers that they should have to address these basic science issues. I think these are interesting issues that certainly stimulate our curiosity, but where do we draw the line in terms of what information needs to be provided to demonstrate that a product, to a reasonable level, is safe?

DR. KATZ: I second that, and I wasn’t trying to imply that an awful lot of mechanistic and fundamental science is the responsibility of a manufacturer. Again, my feeling is that as long as you can do studies in women undergoing elective hysterectomy who volunteer to have
procedures done prior to hysterectomy, you can learn an awful lot of meaningful information. But, certainly, FDA would benefit if there were some stimulation of the science side of this from other agencies.

DR. BLANCO: Yes, I think that is perfect lead-in for us opening it up. I think we have probably discussed number four, unless somebody wants to say something else, and we will have another opportunity. The format will be to open it up to the public and industry and FDA, and then we can come back and finish up discussion if we want to discuss anything else. Dr. Shirk?

DR. SHIRK: One of the questions that wasn’t asked by the FDA and that I might ask myself, and I don’t know how you feel about the panel answering the question, but it is long-term follow-up on these patients. That is a safety issue to me. One of the major safety issues to me is basically the occurrence of endometrial carcinoma and also its detection, and whether the panel would want to make some recommendations as to the post-study follow-up on these patients, and the length of that obviously. You know, beyond three years becomes an onerous thing for them in the premenopausal studies but, yet, three years is not going to tell us anything about this issue in a postmenopausal study. So, do we want to make some recommendations on follow-up on these studies?
DR. BLANCO: I think that is excellent. I think the panel already did that. I think we have said it is very important to find out what is going on with these patients in terms of follow-up and development of endometrial hyperplasia, endometrial cancer and its ability to be detected. I guess the only issue would be the one you brought up. Are you going to require more than three years, and should these patients be followed up longer than three years? I think there will be a high fall-out rate in terms of follow-up, but I think in this particular issue with endometrial hyperplasia and cancer it may be something that needs to be at least attempted. Any other comments from the panel?

DR. ROY: Just two comments. One, I think in the absence of data, if someone wishes to propose to use something they have to do the due diligence to prove that it is safe and effective. So, as hard as it may be for the manufacturers, if they want to go this route they have to prove that it is safe and effective.

MS. DOMECUS: How long do we need to follow the patients to really address this question?

DR. ROY: Well, I was addressing more the issue of design first. My second comment is the follow-up of patients. Three years is inadequate for the purposes of seeing whether endometrial cancer develops. So, you try to
do it as long as you can. I mean, I think that is the only thing I think we can offer from the point of view of the panel, that you really need probably 10, 20 years follow-up for some of these answers to be accrued. Obviously, that is not going to happen in a rigorous fashion but at least we should try to develop a tool to at least recommend that efforts be made to do that.

DR. BLANCO: Any other comments from the panel?

MS. DOMECUS: I just wanted to comment on the 10 to 20 years post-market surveillance. I think that is kind of unheard of in terms of length of time for a post-market surveillance study to be done. If it really takes 10 to 20 years to answer the question, that is going to be pretty burdensome on the manufacturers to do that.

DR. YIN: May I? In cases like that maybe FDA or NIH or some other ways of doing it--

MS. DOMECUS: Right.

DR. YIN: For the manufacturer it may be reasonable maybe three to five years.

MS. DOMECUS: Right.

DR. BLANCO: All right, let's go ahead and poll the public and industry if anyone is interested in coming forth. Please, just remember to state your name and any affiliations, and any support from any industry that may be related to the topic at hand today.
Open Public Hearing

DR. LOFFER: Franklin Loffer, private practice in gynecology in Phoenix, Arizona, Associate Clinical Professor, University of Arizona. I have been using endometrial ablation since the early '80s, T&E by Ethicon. I would hope that the guidelines would focus in on--

DR. BLANCO: I am sorry, what did you say by Ethicon?

DR. LOFFER: Travel and expenses. I am sorry.

DR. BLANCO: Thank you.

DR. LOFFER: I would hope that the guidelines would recognize, as has been pointed out, that postmenopausal patients are not a single group. You clearly have those who are recently menopausal, who went on estrogens and maybe went off for whatever reason, or those that have come in to you and are now wanting to be on estrogen therapy and then decide they don't like it. At the other end of the scale you have the 75-year old who walks in, who has never been on it or has been on it 30 years ago or 20 years ago and didn't like it. Those are two distinctly different groups of patients. We do have a fair amount of experience from a safety point of view in the early postmenopausal patients.

There is a third group which I think is of greater concern to me, those who have been on estrogen therapy and
suddenly start bleeding. No bleeding for a long period of time, and I think that it the group where you are going to see your major pathology come out of.

So, I hope that in the guidelines that are being developed that you not try to treat all postmenopausal patients as being equal.

With regards to a lower age limit, I personally would support an arbitrary figure of possibly 50 years of age. I think if you get below that you are going to start being confused with perimenopausal patients. It is not a problem to take patients off hormone replacement therapy. By and large, these are patients who do not want to be on it. I think it is good practice to take patients off prior to treating them. We give them suppression premenopausally. The best suppression you can give postmenopausally is having them off. So, you could easily have a period of three or four weeks when you could prove by blood studies that they were menopausal.

I think that the inclusion of patients who have only been on estrogen replacement therapy without progesterone agents is totally inappropriate because even if they did do well after ablation, I think not using progesterone in the post-treatment phase is inappropriate and I would hope that the guidelines would strongly emphasize the need for these patients to be on a
progesterone agent.

In closing, my thoughts about the endpoint--I see this more as a safety issue rather than an efficacy issue. The fact that you are taking patients who are not on hormonal therapy because they don't want to be I think means that they provide a perfect endpoint for themselves, and I would support that point of view.

The real issue here is, is it safe and does it alter the number of patients that stay on hormone replacement therapy? Thank you.

DR. BLANCO: Thank you very much for your comments. Anyone else from the public or industry that would like to make some comments for the record? Yes, sir? Remember to state your name and any affiliation and support.

DR. STABINSKY: My name is Seth Stabinsky. I am a gynecologist and the Vice President for Medical Affairs at Novacept.

First of all, thank you for allowing us to get to listen to this discussion. It really was very exciting for me. First of all, to be on the industry side and to be able to participate in terms of listening to colleagues discussing the treatment of postmenopausal women with these revolutionary sorts of technologies.

The first issue I hope that the committee will consider when they do their guidance document--Dr. Blanco
brought up the point before that we need to use drug therapy as probably the alternative. The idea of using Rollerball ablation as an alternative in this group of patients, to me, seems to be somewhat contradictory in that there is some degree of risk in endometrial ablation, particularly in a group that might be cardiac compromised, etc., and the fluids that we need to use with typical endometrial ablation. So, I would really strongly urge the committee to consider not using Rollerball as the other arm for this study.

In searching the literature, if people are continued on their continuous hormone regimen for between one and two years, generally there is a 90-95 percent incidence of amenorrhea. Of course, those are drug company-sponsored studies so, you now, will it really be 90-95 percent at one to two years? We are not sure. But it certainly is a very high rate. The problem is that women quit their hormones very early in the game. So, I would hope that we would be able to find in the guidance document a way of being sure that the patients are appropriate for treatment, such as with some hormone manipulation, but that we keep that to a reasonable number of months and therapeutic agents for those patients to be able to be willing to participate in a study.

And, then that we consider the fact that in terms
of a gold standard, as Miss Young was searching for before when you talked about using Rollerball ablation, the gold standard really could be drug therapy. If people would stay on their hormones for long enough their bleeding will go away if they stay on continuous hormone replacement. The problem is that they won't stay on it. But it isn't just an issue of quality of life; it is an issue of their bones and their heart. So, it is actually, as you are all aware, very important to keep them on their hormones.

In terms of being able to measure reduction in bleeding and using the patient as their own control, the problem currently is that there is no--the Higham study, and thank God for Jennie Higham for all of us who have been developing endometrial ablation products in the premenopausal women, there is nothing similar in the postmenopausal group of women, and obviously it would be much more difficult to be evaluating quantity of blood lost in someone who is just having spotting to begin with, but that spotting is on a daily basis and annoys them. So, again, the idea of looking for a way to say that, you know, women who are willing to now stay on their hormone replacement would be a success as long as there weren't other reasons for them quitting, as Miss Domecus mentioned.

Finally, in terms of the extirpated uteri and pre-hysterectomy uteri, the pre-hysterectomy uteri--and I am
sure the FDA will confirm for all the industry companies who have worked in this area that they are extremely difficult to obtain, to do pre-hysterectomy cases. You are asking patients, and especially now an older woman who is undergoing a hysterectomy, to have to have temperature monitors, cirrhosal monitors put on their uterus and delay their surgical case. So, doing actual in vivo cases pre-hysterectomy is extremely burdensome and very difficult and, frankly, if any of our families were undergoing hysterectomy, since they are not going to get any benefit from that, one would have to ask what is the value to the patient in participating in a pre-hysterectomy study. So, it is just something to consider in terms of pre-hysterectomy uteri.

Then finally, in terms of the extirpated uteri, the one risk that I see, and perhaps my industry colleagues will throw things at me, but the risk that I see in case of the extirpated cases is that there is some degree of risk. When we ablate and extirpated uterus there is some degree of risk that we have now damaged the pathologist’s ability to read that uterus for the potential of future cancer. So, perhaps in your guidance document you can talk about the need to hysteroscope that uterus in the lab and do adequate sampling to be sure that there wasn’t a missed occult cancer before it gets treated in the laboratory.
Finally, in terms of long-term follow-up, I think that Dr. Yin's suggestion is a marvelous one and that perhaps organizations like the American College of OB-GYN and the AGL could get involved, as well as the NIH because the products won't get out there to help the patients that we want to help if we need to do a 20-year follow-up, and the difference, frankly, between three and five years of follow-up, as all of you are aware--by following these patients for five years we are not going to pick up any more endometrial cancers. It is a 20-year disease and so I think leaving it at the three years seems to make reasonable sense to me. Thank you for allowing me to comment.

DR. BLANCO: Thank you very much for your comments. Would anyone else like to make any public comments? Please? Remember to identify yourself, and your affiliation and support.

DR. LUOTO: Thank you, Mr. Chairman. My name is Dr. Joanne Luoto. I am with the National Institute on Child Health and Human Development at NIH. I have been very interested in the discussion.

Certainly in the latter part of this morning a number of questions were raised that don't have answers, and it is appropriate, I guess, for me to mention that the National Institute on Child Health is actually beginning to look at the issue of endometrial ablation technologies. In
fact, my branch, which is the Contraception and Reproductive Health Branch, is sponsoring a small working group tomorrow to discuss what the research needs are in the area to determine if it fits within the NIH and specifically the NICHD agenda. That is an open meeting. It has not been widely publicized because it will be a very preliminary examination and development of a document which defines areas that our invited experts feel are the most critical research gaps. This is not a meeting that will relate to industry, regulation or approval. It is, in fact, a research-directed meeting and, as I indicated, very preliminary.

For those of you in the audience or on the panel might like to have more details, you can either speak to me later or you can call area code 301-496-4924. The location of the meeting is approximately a mile from here, and it will start at 8:30 tomorrow morning. I think that about covers it. Thank you.

DR. BLANCO: Thank you very much for your comments, and I think from what the panel said we should be quite happy that there is some interest in pursuing this as a line of research.

MS. YOUNG: May I make a comment?

DR. BLANCO: Please.

MS. YOUNG: I would ask a question of the person
who was just here, please. I think it is very fortuitous that you were here this morning and that you are having this meeting tomorrow. Are you planning to convey some of the points that were raised this morning in the discussion, and take those back to the meeting tomorrow?

DR. LUOTO: Yes, yes I will. The actual format of the meeting is fairly short summary presentations by the invitees in the morning. The afternoon is dedicated, except for a brief presentation by the agency for health care promotion on their two community research projects, looking at ablation as an alternative to hysterectomy and except for FDA's presentation on regulatory issues relating to ablation technologies, other than that the afternoon will be dedicated to internal discussion among the invitees and, of course, as appropriate the proceedings and issues that resulted from yesterday and today will be discussed.

I probably should have added for the record that I have no industry connections whatsoever.

DR. BLANCO: Thank you very much. Any other comments from the public? Yes, please?

DR. GRANGER: My name is Dr. David Granger, and I am an Associate Professor and Director of the Division of Reproductive Endocrinology at the University of Kansas in Wichita. My travel expenses were paid by Ethicon.

First of all, I would like to commend the panel on
their very artful deliberations of this very difficult
topic. It is something that we have put a lot of thought
into also. I believe that Dr. Katz really alluded to the
difficulty of the study design when he stated that there was
a large abundance of postmenopausal uteri available for **in**
**vitro** inspection. In fact, patients that are motivated
enough to continue hormone therapy and that continue
bleeding will generally have a hysterectomy as the solution
to their problem.

To suggest one study design, not one that I am
personally proposing, but one could take this group of
patients that failed hormonal therapy and randomize them to
either hysterectomy or endometrial ablation with continued
hormone therapy. I believe there would be a lot to learn
from that study on quality of life issues and, clearly,
hysterectomy patients are going to be amenorrheic so I am
not sure about bleeding. But there is also probably a lot
of economic information that would be available from a study
like that.

However, I believe that Dr. Blanco alluded to a
study design which I think would be appropriate, and that is
a crossover study. Dr. Roy mentioned that these patients,
for inclusion, should have failed modifications of their
hormone regimen. If we accept that as a study group, that
study group could be randomized to either ablation or some
further change in hormonal therapy. After a prescribed period of time, the failures in each group—and as Dr. Shirk also alluded to, there won’t be 100 percent amenorrhea in the ablation group. You could cross those patients over into change in hormonal therapy for patients that failed ablation, or ablation for the patients that failed hormonal manipulative therapy. I think that that might be a way to get our hands around this very difficult problem. Thank you.

DR. BLANCO: Thank you very much for your comments. I don’t believe there are any other public comments. Does any representative from the FDA like to make some final comments, and then the panel will have a chance to do any discussion that they feel is necessary. Mr. Pollard, would you like to add a few comments?

MR. POLLARD: Thank you, Dr. Blanco. I think the only comment that I would add at this point is that we have a very definite plan to take all the comments from the panel, and the audience as well, and really sit down and try to sift through a lot of the difficult issues that you have discussed and develop some draft guidance and bring it back to the panel to see if this is kind of what we have in mind.

DR. BLANCO: Thank you. Any further comments from anyone on the panel?

MS. DOMECUS: Actually, I wanted to make a comment
that wasn’t directly related to any of the questions, but I
still want to comment on the distinction I have heard today
and several times before when we have talked about these
devices on medical indications versus "cosmetic"
indications. The term cosmetic actually kind of hits me the
wrong way. It kind of hits me the same way as when people
say PMS is all in a woman’s head. I think it tends to
trivialize the importance of the quality of life issues
involved here. So, I just wanted to comment on that term.

Also, there seems to be an assumption that a
cosmetic indication is not one that the manufacturers would
pursue, and I just want to point out the FDA does regulate
plastic surgery devices. So, cosmetic indications are
within their realm. I hope that even though we focused more
on a medical indication today that we are not telling
manufacturers that they can’t pursue a cosmetic indication
for these devices. Obviously, you would have to change the
risk-benefit ratio that they would have to support, but in
all the meetings we have had on these devices there seems to
be kind of a pooh-poohing of the cosmetic indication, and I
don’t know that that should be off the list for
manufacturers to pursue.

DR. BLANCO: Any further comments? If not, I want
to thank the panel for another very interesting half day, a
very interesting discussion. I would like to thank everyone
at the FDA, as well as everyone from the public and industry for all their comments.

We are actually finishing a half hour early. We hope we can continue this tradition of getting all the information out but finishing early. We will reconvene for the afternoon session promptly at one o'clock. Thank you.

[Whereupon, at 11:30 a.m., the proceedings were recessed, to be resumed at 2:45 p.m.]
AFTERNOON PROCEEDINGS

Introduction

DR. BLANCO: We have a lot to do this afternoon, so let's go ahead and call the meeting to order. Let me remind the audience that there is a sign-up sheet in the back of the room, if you would please make sure to sign in so that we have a record of who is here and who participated in the discussions.

We will have some comments from the audience. Please make sure that you are recognized prior to starting to speak. Let's not have any outbursts. You should identify yourself, come to the microphone so we can record what you say; identify yourself; give a full conflict of interest disclosure, including whether you have been reimbursed by any industry that has an interest in the discussions that will go on this afternoon--travel, per diem, consulting or any other involvement with the company.

I think since we have had some changes among the panel members and this is a totally different topic from what we did this morning, I thought that we should re-introduce ourselves to make sure that everyone in the audience knows who the panel members are.

I am the chairman of the panel. I am Jorge Blanco. I am a Professor and Associate Chairman of the Department of OB-GYN at the University of Florida,
Pensacola, and the Medical Director at Sacred Heart Women's Clinic in Pensacola, Florida.

DR. NEUMANN: I am Michael Neumann, from the Joint Program in Biomedical Engineering of the University of Tennessee, Memphis, and the University of Memphis.

DR. ROY: I am Subir Roy, Professor of Obstetrics-Gynecology, University of Southern California School of Medicine.

MS. YOUNG: I am Diony Young. I am editor of the journal *Birth*, and I am the consumer member of the panel, and I live in Geneseo, New York.

DR. YIN: Lillian Yin, Director, Division of Reproductive, Abdominal, Ear, Nose and Throat and Radiological Devices, Center for Devices and Radiological Health, FDA.

MS. DOMECUS: Cindy Domecus, Senior Vice President of Clinical Research and Regulatory Affairs for Conceptus, and I am the industry rep. on the panel.

DR. ALLEN: I am Michelle Allen, Assistant Professor of OB-GYN, NYU School of Medicine, Director of Ambulatory Services, Bellevue Hospital.

DR. CHATMAN: Donald Chatman, generalist in obstetrics and gynecology in Chicago, Clinical Associate Professor, Northwestern University.

DR. SHARTS-HOPKO: I am Nancy Sharts-Hopko,
Professor in the College of Nursing at Villanova University, Villanova, Pennsylvania.

DR. KATZ: I am David Katz. I am Professor of Biomedical Engineering and Obstetrics and Gynecology at Duke University.

DR. HARVEY: I am Elisa Harvey, the Executive Secretary to the Obstetrics and Gynecology Devices Panel, FDA.

DR. BLANCO: Thank you. The FDA press contact, if you are interested in contacting someone, is Dr. Yin, who is right at the end of the table here.

We do have a very full agenda on an important issue. Therefore, I am going to ask that any comments that you make be brief and concise, and I would now like to introduce again Dr. Harvey who has a few items for us.

DR. HARVEY: Just a couple of housekeeping notes. If you could please clean up after yourself after the meeting, that would be very helpful to us. To the members of the panel, if there is anyone who needs transportation after the meeting and has not already signed up on the sheet in the sign-in area, if you could do that at the break they will arrange to have transportation, hopefully, waiting for you or shortly after the meeting is finished.

DR. BLANCO: Thank you. At this point I would like to introduce Mr. Colin Pollard. Mr. Pollard is the
Chief of Obstetrics and Gynecology Devices Branch, Center for Devices and Radiological Health, in Rockville, Maryland. He will be doing an introduction and general update, and giving us some sense of where the panel discussion is to begin.

**Introduction and General Updates**

MR. POLLARD: Thank you, Dr. Blanco. Members of the panel, distinguished audience, this afternoon the panel is being asked to consider what here at FDA we call a labeling template for fetal vacuum extractors and, in this context, we plan to develop this as a guidance document that will be available to manufacturers of fetal vacuum extractors for use of their own device.

To facilitate this discussion, we plan a couple of presentations beforehand to talk to you about our recent experience over the last year with an ad hoc committee we formed to look at an increase in the reports from our MDR program, the Mandatory Device Reporting program, for this kind of device.

That committee made a couple of recommendations. Actually, it made six or seven recommendations, one of which was to issue a public health advisory, of which you have a copy in your folder. That was issued May 21st. Another recommendation from that ad hoc committee was to provide specific labeling guidance to manufacturers of fetal vacuum
extractors, especially with regard to the areas of indications for use and contraindications for use.

Towards that end, we have asked two of our clinicians to provide you with information, first of all, Dr. Danica Marinac will give you an overview of the ad hoc committee exercise and the public health advisory that was issued in May. Following that, Dr. Diane Mitchell will essentially walk you through the labeling template that we prepared, and for which a set of discussion questions were crafted by FDA staff to facilitate the discussion.

In your folder, on the right-hand pocket, besides the agenda and the questions, you will find hard copies of the overheads used by the presenters, some example labeling currently in use for fetal vacuum extractors, a number of indications for use forms from recently cleared 510(k)s for these kind of products, as well as the labeling template itself.

So, after the open public hearing that immediately follows my comments, Dr. Marinac and Dr. Mitchell will give you their presentations.

Open Public Hearing

DR. BLANCO: Thank you, Mr. Pollard. We will go ahead and open it to the public speakers. I would remind the public speakers that each of you will have five minutes, and we will try to stick very closely to the length of time
for the agenda. Also, if you have not already done so, if you would please give a hard copy of your overheads, slides and written statements to the FDA, Mr. Yung Pak, who will be happy to receive those and they can become part of the formal proceedings.

The first scheduled speaker that we have is Dr. Larry Gilstrap, representing the American College of Obstetrics and Gynecology, and I don't see Dr. Gilstrap here. Is someone representing him?

[No response]

Well, we will reschedule him later on. We will see if he comes later on. The next one is Dr. Aldo Vacca, Caboolture Hospital, Brisbane, Australia. Dr. Vacca, are you here?

DR. VACCA: Yes, I am.

DR. BLANCO: Thank you very much. Will you please introduce yourself and tell us of any conflict of interest and support.

DR. VACCA: Yes, my name is Aldo Vacca. I am an obstetrics from Brisbane, in Australia. I have an interest in vacuum extraction that dates back for more than 30 years, and I have no support or affiliations with any of the members of the industry.

[Slide]

As I mentioned, I made a life-long study of vacuum
extraction, dating back for more than 30 years, and from the very beginning of the modern era of vacuum extraction, which dates back to a little over 40 years, there have been reports of adverse outcomes associated with this device, this one dating back to 1962.

So the warning in the advisory is certainly very timely but is certainly not new. What is new and what I like about the advisory is that there is a commitment to minimize the risks.

I would like to present just two ways in which I think we can achieve this goal. The first is in the area of vacuum delivery technique. As you can see, vacuum extraction is much more than the device itself. It consists of a whole range of skills that need to be required by the operator. But I am just going to concentrate on one crucial aspect, and that is the correct positioning of the cup on the baby's head.

Many of the injuries that are associated with this delivery method are associated with an incorrect cup application but, of course, the type of device that we use may well determine whether we can achieve a correct cup application.

[Slide]
Let me explain. We have a problem in the occiput posterior position, as I have illustrated here, that is, when the face is uppermost, because the design of many of the cups in popular use today, and I have shown an example here, make it extremely difficult, if not impossible, to achieve a correct application when the cup is in this position. The problem arises because the stem of this particular cup design, as you can see, comes up against the maternal tissues at the outlet of the birth canal so that the aim of attaching the center of the cup here, to the most dependent part of the fetal head, is just not possible. So, we have to settle with a less than ideal cup application.

[Slide]
The point that I want to make here is that we need a cup--and this was produced more than 25 years ago--a cup that has been especially designed for use in this situation where the tubing and the body of the cup are in the same plane. So, the cup may be introduced into the birth canal and advanced towards and over the correct portion of the baby's head so that a correct application may be achieved. This is one area that I believe we need to address urgently.

[Slide]
The other area that I would like to touch on is in the selection of patients who are suitable for this procedure. I would like to describe the process that I use
to select the women who are suitable and those who are not. I look for these key obstetrics factors, namely, arrest of descent, station of the head, the condition of the fetus, the degree of molding, the position of the baby's head in the pelvis. For station and position I use the ACOG recommendations.

The other key factor that we must always consider in selecting patients suitable for vacuum extraction is the level of skill of the operator. I have put here in brackets, "C" being the operator who has acquired all the basic skills; "A" being a highly trained operator who has achieved skill in all aspects of vacuum extraction.

So, by carefully evaluating the interactions between these key obstetric factors, it is possible to select those women in whom vacuum extraction is appropriate from those where it is not. Of course, it is not set in concrete. You can select your cut-off point at any stage along these obstetric circumstances. I believe that all of these circumstances are appropriate for vacuum extraction provided all the criteria have been established.

[Slide]

Finally, it is our challenge to make this procedure as safe as possible for mothers and their infants. I have mentioned but two ways in which we might attempt this, but the way toward a better outcome has been well
documented. The bottom line is training and more training. Can I ask you, how many of you would allow someone to perform a forceps delivery without appropriate training? Why shouldn’t we expect the same for vacuum extraction?

Thank you.

DR. BLANCO: Thank you, Dr. Vacca. The next speaker is Tracy Biltz--forgive me if I am not getting that correctly--with Prism Mityvac. Please remember to state your name, your affiliation and any support from industry.

MS. BLITZ: I do have overheads too. May I stand up there?

DR. BLANCO: We can do the overheads for you. It would be better for you to be at the microphone.

MS. BILTZ: In the essence of time, I will just tell you that I am Tracy Biltz--

DR. BLANCO: You have to use the mike.

[Slide]

I am Tracy Biltz. I am the Director of Medical Products for Prism Enterprises.

[Slide]

We are the originators of the soft-cup design with over twenty years of vacuum extraction experience, and we provide a full product line with two different cup styles, a bell shape which is basically a bell, as you saw on Dr. Vacca’s slide, and a mushroom, which is truly a mushroom
shape. You saw that also on Dr. Vacca's slide.

[Slide]

As I understand, our goal here today and our primary objective is a healthy outcome, that being a high Apgar score for babies and no complications or very limited complications for the mom.

The effectiveness towards meeting our goal can only today be measured by the reported incidence. Right now, we are looking at 1 in every 45,455, which gives us about 0.00002 percent. Clearly, since the advisory has been issued, we are seeing a little bump in the MDRs that have been filed. And, I do applaud the FDA, at least from my perspective. What we are seeing is that people are being more cognizant of the complications and monitoring the babies closer afterwards. So, we will see an increase in the incidence reported but, hopefully, we will not see the severity increase.

Another thing that I would like to impress upon all of us is that we develop best practice guidelines for all assisted delivery devices. As Dr. Vacca mentioned briefly, we would all expect that forceps and other devices that are used to assist deliveries also might be reviewed for how we can prepare operational guidelines to assure the safety of those devices as well.

[Slide]
This slide is the current use of vacuum extraction devices. It is estimated in about 10 percent of deliveries. In brief, indications are fetal distress and prolonged second stage and I will talk a little bit more about that in a moment. Preferred assisted device with transverse arrest. That was documented in a research study by Dr. James Bofill in December of 1996. It is estimated to be used in about 5-7 percent of cesarean deliveries.

On this slide you see the use of vacuum assisted devices in cesarean deliveries, if we can talk about that for just a moment. Since you already have the slides ahead of you, I will go on. Prism has no reported incidence of to date of any injury that has occurred when a vacuum extractor has been used during a cesarean section. The indications have been stated as a high floating head, which can clearly be stated as an elective repeat cesarean. The advantages here are that you do not have to use extreme fundal pressure to push the baby down and in a position that can easily be extracted. You do not have to use your hands in trying to grab the head and to extract the baby out, which can be slippery and difficult. So, the advantages are as stated. It decreases the uterine manipulation and the risk of extensions into the lower uterine segment, thus reducing the risk of hemorrhage for the mom.
We are all driving for a healthy outcome, and I have just a few bullet points as to how we hope to accomplish that: Use appropriate indications. We have stated them, and on the back of this brochure you will note that we have recommended guidelines, as well as indications. You also should have been copied on our operational guidelines that are included in our sterile packaging. These are the indications that we use today: fetal status, failure to deliver spontaneously, maternal need to avoid voluntary expulsive efforts, any kind of cardiac or stroke risk for mom, and inadequate expulsive efforts.

If you flip to the next slide, the healthy outcome also is driven by ensuring proper placement. Dr. Vacca, again, did talk about this. That placement should be on the medial flexing point to help minimize the diameter of the head coming through the pelvic outlet. Also, you can state it as a mid-sagittal position over or near the posterior fontanelle.

I did review the template and noted that you all have clearly stated that. Also, I noted that we should allow the manufacturers to provide product specific operational guidelines, as you will note. Because of the cup shapes and designs, it is very important that we are
allowed to tell them how to get the best results and to
ensure safety. You all should have the operational
guidelines, if you need any reference on the bell versus the
mushroom shape.

[Slide]

My last slide is a healthy outcome driving that
goal. We need to ensure proper training and use; carefully
monitor the post-vacuum assisted neonate. I really do
applaud the FDA. As a director of medical products and as a
nurse, I clearly have seen a result from the FDA with the
documentation in the hospitals.

Also, in closing, to continue to support the use
of vacuum assisted delivery devices that help attain our
mutual goal of achieving a healthy outcome.

If you have any questions, I will be more than
happy to take them, but thank you for your time.

DR. BLANCO: Thank you for your comments. We
appreciate comments for the record. Next to speak will be
Sam Johnson, with Utah Medical. I will remind you to
identify yourself, any support and your relationship with
industry.

MR. JOHNSON: My name is Sam Johnson. I am the
marketing manager for the obstetrical products line for Utah
Medical Products, and we are a supplier of the cups to the
industry.
An outline of my points of discussion has been distributed by Dr. Harvey, and there are two basic areas. One is a history of CMI and the second would be issues related to safe utilization of the vacuum systems.

Utah Medical acquired CMI in July of 1997. So we have owned them for approximately a year and three months now. CMI has focused on vacuum extraction since 1982, when they originally began as a distributor for Mityvac, then beginning in 1988 as an independent manufacturer. Since 1988, CMI developed vacuum extraction products on which it holds five patents, the most significant of which is related to soft silicone bell-shaped cups.

Although over 40 percent of the cups used in the U.S. are mushroom shaped, by our estimate, over 97 percent of cups sold by CMI are bell shaped. CMI has sold almost one million bell-shaped cups over the last five years, which we estimate to be four percent of total births, with no MDRs prior to the FDA advisory and no product liability lawsuits which resulted in a judgment against CMI ever.

In light of that, we feel that there are two major areas associated with safe utilization. One is physician technique. To assist physicians in use of a proper technique, Utah Medical has provided several things for educational purposes. Again, these should be included in the handouts.
The first is an expanded instructions for use, which constitutes four pages of instructions and one is included in every box of product.

Secondly, a condensed instructions for use on an 8.5 by 5.5 card, printed front and back, in each container or each pouch of vacuum cups.

Thirdly, we have the CMI instructional booklet which is sent to each of our customers, and is our most comprehensive written document to date.

Then, fourthly, we have the instructional video which is sent upon request to each customer. The video details an actual vaginal delivery, as well as a cesarean delivery, for educational purposes.

In light of the physician technique issue, we think that style of equipment is also a major factor currently in the safety of the devices. One concern, and the first concern is, of course, that the pump be reliable and provide accurate measurements of the actual vacuum force. This has to be emphasized.

Also, in light of possible failures to abort the actual vacuum delivery attempt and an unwillingness to give up on the procedure when things aren’t progressing as they should, we feel, in the near term, that soft bell-shaped cups will release from the fetal scalp sooner than a mushroom-shaped cup when an excessive or misdirected or
otherwise inappropriate force is applied and, therefore, the
cup will provide better protection to the infant from
serious injury.

Are there any questions?

DR. BLANCO: Thank you. Our next speaker is Dr.
Larry Gilstrap.

DR. GILSTRAP: I am Dr. Larry Gilstrap. I am the
Chairman of the Department of Obstetrics and Gynecology,
Houston Medical School, and I am representing the American
College of Obstetricians and Gynecologists as the past chair
of the committee on obstetrics. I have no commercial ties
with any of these devices, although I have authored two
textbooks that talk a lot about these devices, but I have no
commercial connections.

The American College would first like to thank the
panel for the opportunity of being able to present our
viewpoints, and as care givers primarily for women and their
unborn children, we certainly have concern also about
reports of the morbidity that has been brought forth by the
FDA. However, we would like to make the following points:

One is that the number of reported deaths and
injuries associated with vacuum deliveries is relatively
small considering the total number of deliveries in the
United States each year. Although there may be an under-
reporting of the morbidity associated with these devices,
the exact incidence of this morbidity is difficult, if not impossible, to actually calculate considering we really don’t know what the denominator is. We have a lot of estimates as to how often these devices are used, but we really don’t have any hard numbers, and the frequency of vacuum delivery, from the literature, ranges from 0.3 percent to as high as 6.2 percent.

We have no information on these injuries regarding the level of training and expertise of the operators; no information as to the type of devices used; no information as to the station and position of the fetal head at application of these devices, and this is an area that I certainly have concern about, the general impression that it might be safer to put a vacuum device on at a higher station than forceps, which is certainly not true and there is no evidence that that is true. We have no information as to the indications for these procedures; no information as to the number of attempts or failures in these reports; and, no information as to the frequency of non-physician or non-obstetrically trained individuals providing these deliveries; and, no data that the device per safety and efficacy is at fault.

We would like to make the following recommendations regarding future labeling, and most of these have been included in the preliminary labeling that I have
The operator or teacher must be appropriately trained, experienced and skilled in the use of these devices.

These devices should be utilized only for specific obstetric indications as opposed to elective use.

Essentially, the indications are the same as for forceps deliveries. Vacuum deliveries should be classified according to the classification by the American College of Obstetricians and Gynecologists, first published in 1988 and reaffirmed in 1994.

The same prerequisite for forceps applications should be applied for vacuum applications, the same applications; the same prerequisites.

Half vacuum applications should not be attempted. Mid vacuum applications carry the same risk as mid forceps deliveries and should not be attempted, except by the most skilled operators, and only in certain specific emergent conditions.

Specific guidelines for pressure should be adhered to. The clinician must be willing to abandon such procedures if they do not proceed well and easily.

The risk of routine vacuum application at the time of cesarean delivery is unknown and should not be done routinely.
Again, the American College of Obstetrics and Gynecology would like to thank the panel for the opportunity to speak before it.

DR. BLANCO: Thank you, Dr. Gilstrap. Those are the folks that we have registered that desired to speak. Are there any other public members or industry members that would like to be heard at this time? If not, we will move on with the next part of the agenda. The next part of the agenda are the FDA presentations. I would like to introduce Dr. Marinac, who is in the Division of Post-Market Surveillance, Office of Surveillance and Biometrics. I hope I got your name right.

FDA Presentations

DR. MARINAC-DABIC: Hi. Yes, my name is Danica Marinac-Dabic.

I am with the Epidemiology Branch of the Office of Surveillance and Biometrics, and I also was a member of the ad hoc committee that looked into the issue and all the reports that we have received related to the vacuum assisted delivery devices.

As you know, on May 21st this year FDA issued a public health advisory indicating the need for caution when using vacuum assisted delivery devices. The goal of my talk
today is, number one, to explain what prompted the FDA to issue this public health advisory; number two, to explain how the process within the FDA worked; how the ad hoc committee came to its recommendations and what the recommendations were, and what parts of those recommendations we have completed so far.

[Slide]

Over the past four years, FDA has received reports of 12 deaths and 9 serious injuries among newborns on whom vacuum assisted delivery devices were used. This overhead represents the distribution of the number of reports by year when the event occurred, starting from year 1983 which was the year that we can go back to in our database, and ending in year 1997, and all of these reports were included in the public health advisory.

As you can see, in year 1983, '84, '85 we had only one report. Then, in '86 also we had one report. In '87 we had zero reports, as well as in '88. Also in the year 1989 we again had one report. In 1991, one report; in 1992 one report. I would like to mention at this point that this year, when the user facility reporting came into effect we did expect to receive more reports at that time.

If you follow this slide, we can see that in year 1993 we received two reports. Then, all of a sudden, in year 1994 we received six reports of the adverse events
associated with the vacuum assisted delivery devices. In 1995 we received three; in 1996, again six reports, as well as in year 1997.

[Slide]

How our Center responded to this issue--first of all, we had formed a working group. Then that working group became an ad hoc committee. I have listed on this slide the steps that we went through, and these activities were undertaken by the committee members. I would like to point out that on this committee we had physicians. We had biomedical engineers. We had statisticians, epidemiologists. We also had nurses, analysts, and we tried to represent all possible angles so that we could look into this issue.

The first thing that we, of course, had to undertake is to look into the adverse report database. This is what I actually presented in a previous slide.

[Slide]

I just wanted to let you know that we identified the different types of events that were reported to us. As you can see here, I have listed on this slide the distribution of the events by type of event, by death and injury.

[Slide]

Based on information that we could find in those
reports, we realized that we cannot point really toward one particular device, nor at one particular manufacturer, nor at one specific type of cups. Not to mention that in our database we did not have really have access to the most critical information about the clinical situation that surrounded the application of this device.

So, we realized we needed to go externally and try to do a literature review to find out what the exact use of this device is, and the prevalence of the use of vacuum assisted delivery devices is, and what the rate of complications is. We also performed a labeling review. We sent letters to manufacturers, those that had responded to us, and then invited them to talk to us about our concerns.

We performed a dialogue with the users. We invited obstetricians to talk to us about their experience with the device, and also this dialogue with users was also conducted on different levels. We went and investigated the user facilities when the three most recent incidents were reported to us.

Finally, we also realized that we cannot act alone, and we needed to consult with professional organizations, including the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, American College of Nurse Midwives, American Academy of Pediatrics.
[Slide]

As I said, we wanted to make sure that we understand what the entire picture is. So, this is the most recent estimate nationally that we could obtain from the National Center for Health Statistics that was published in 1997, and which reflected the increase in the use of vacuum assisted delivery devices from year 1989. It was 3.5 in 1989 and, as you can see, in year 1995 it was 5.9. These percentages actually reflect the percentages of the entire number of deliveries in the United States. In year 1989 we had 3.5 percent of vacuum use out of all numbers of deliveries versus 5.9 percent in year 1995.

It is interesting that during the same time the use of forceps decreased from 5.5 in year 1989 to 3.5 percent in 1995. At the same time, the rate of cesarean section decreased from 22.8 percent in 1989 to 20.8 percent in year 1995.

[Slide]

As a group, we have concluded after reviewing the literature, reviewing the reports, discussing with manufacturers, users and professional organizations that the possible reasons for an increased number of adverse event reports associated with vacuum assisted delivery devices could be the following: Increase in use of the device, and I have just pointed out the national estimates of that.
Also, we realized that some changes in the reporting system might have contributed to the increased number of reports. Predominantly, I have in mind the use of user facility reporting data which became effective in 1992. Also, we cannot neglect the potential under-reporting in previous years. Also, finally, the real increase in the incidence rate of adverse events.

[Slide]

This slide represents the Center’s ad hoc committee recommendations. As you can see, public health advisory is only one of them. In addition to that, we have concluded that we need to continue the dialogue with the American College of Obstetricians and Gynecologists.

We also need to publish an article in the FDA’s column in JAMA, and we did that in the July issue of JAMA where we basically summarized the public health advisory. Also, we decided that we need to look into the promotional claims regarding the ease and safety of vacuum assisted delivery devices. We thought it is important to invite manufacturers to discuss the agency’s concerns regarding the adverse effects of the device, and also to revise the labeling of the devices to include warnings regarding specific complications, the thing that we will be discussing today and, finally, to propose and encourage academic, user and/or industry research of complications.
associated with the device.  

[Slide]  

Just briefly because I know that all of you do have a copy of the public health advisory in your folders, but just to point out one more time what the major purpose of this advisory was: To advise the medical community that the vacuum assisted delivery devices may cause serious or fatal complications, and also to provide guidance on how to minimize the risk.  

[Slide]  

These are the major complications associated with the device. I know that all of you are familiar with those. I just need to put those on a slide one more time. Those are subgaleal hematoma or subaponeurotic hematoma, and intracranial hemorrhage that, depending on the location, can be subdural, subarachnoid, intraventricular, or intraparenchymal.  

[Slide]  

I am not sure how clear this is going to be, but you also have copies in your handouts. This slide actually shows the location of the injury when subaponeurotic hemorrhage occurred. Basically it is between this dense membrane and periosteum. What is important to point out here is that this doesn’t contain any boundaries so if the injury of the emissary vein were part of that region, then
the bleeding can spread and the volume of blood is almost
the same as the fetal blood volume. So, that is why we felt
it is important to point out the most dangerous and fatal
complications of the use of the device.

[Slide]

This is the same thing. On the right side you can
see subgaleal hematoma, and just as a comparison I included
cephalhematoma to make sure that we understand the
difference. Cephalhematoma is within the periosteum and
that is why it is usually limited by the boundaries of the
bones. It never has that potential to really accommodate
that much blood.

[Slide]

Finally, these are the specific recommendations
that we included in the public health advisory. The first
one is to use a vacuum assisted delivery device only when
specific obstetric indication is present.

Also, to make sure that persons who use this
device are versed in their use, and that they are aware of
indications, contraindications and precautions.

Before using the device, always read and
understand instructions. Alert those who will be
responsible for the neonatal care that the vacuum assisted
delivery device was used in that delivery.

Also, educate the neonatal care staff about the
complications of this device, and, of course, report all the adverse events associated with this device to the FDA.

Thank you.

DR. BLANCO: Thank you, Dr. Marinac. Dr. Diane Mitchell, Obstetrics and Gynecology Devices Branch, Office of Device Evaluation, will now make a presentation.

DR. MITCHELL: Good morning.

[Slide]

Today, what I would like to present is a labeling template that we have developed for fetal vacuum extractors. In your packet is also this labeling template and everything that is mentioned in here is going to be brought up on the overheads.

[Slide]

The Code of Federal Regulations, 801.109, labeling for prescription devices, lists the following points that need to be mentioned when producing a labeling document: To include indications, methods, frequency and duration of administration, contraindications, side effects and hazards, precautions and warnings, and information for use.

The Code mandates that the FDA require adequate labeling to provide a trained user with the information needed to use that particular device properly. It is important also to understand that this information does not need to be in its entirety for use of the device.
The labeling template is a guidance for manufacturers to use when labeling a device. Today, during my talk you will hear me use the terms guidance and template. I will be using them interchangeably.

The purpose of developing a guidance is to perform a critical review of the labeling and standardize the labeling in order to make the information helpful to the user so as to optimize proper use of the device. The template is to be used as a basis for the manufacturer to develop his or her own labeling.

This overhead illustrates the table of contents in the labeling template guidance. The areas that have asterisks are the ones that have clinical significance that I will review today. They include indications and usage, contraindications, warnings and precautions, adverse events, patient counseling information, and clinician use information.

The indications that the FDA has chosen in the Branch are listed above. Now, before I say what they are, I just want to take a minute to explain our rationale. Our goal was to condense the indications into a few broad categories. In the next few slides you will see what are
considered to be subcategories of these particular indications. What I hope the purpose of the discussion today will be is to not only look at these indications that we have listed, but the subcategory indications, and make sure that we have the right group of indications and, if not, revise those.

The indications were taken from a combination of approved fetal vacuum extraction devices and a search of the literature. The first indication, prolonged second stage of labor, can be divided into maternal, fetal and maternal and fetal.

Maternal indications for prolonged second stage of labor can be thought of to be inclusive of maternal exhaustion, lack of cooperation, excessive analgesia, inadequate contraction activity leading to failure of descent or rotation, uterine inertia.

Fetal indications could include dystocia; dystocia due to lack of flexion coupled with malposition in the absence of cephalopelvic disproportion; and occiput posterior presentation.

An indication that was felt to be both maternal and fetal, failure to deliver spontaneously following and appropriately managed second stage.
The indication of non-reassuring fetal heart rate pattern was felt to be inclusive of the subcategories of fetal distress as evidence by a significant deceleration persisting well after the contraction. Fetal compromise was related to intrauterine growth retardation, IUGR, oligohydramnios preceding labor. Fetal compromise as related to cord entanglement, acute fetal distress and presumed fetal jeopardy.

The indication of maternal medical illness that prohibits adequate second stage of labor. We felt subcategories of that included need to avoid voluntary expulsive efforts; indicated shortening of second stage; medical illness that mandates a shortening of the second stage of labor; and sudden maternal compromise.

The indication of cord prolapse and abruption did not have any specific subcategories. They were put up there as separate indications only because in the literature they would be mentioned in the context of these may be appropriate indications to do a vacuum extraction with an incompletely dilated cervix, or at a level higher than outlet presentation.
So, there are other indications that we chose not
to list. However, we would appreciate a discussion of them
as to whether they would be appropriate or not. These other
indications include cesarean section; borderline
cephalopelvic disproportion; incompletely dilated cervix;
mid or high pelvis extraction, recognizing that these don’t
go together; elective and unengaged fetal heart.

[Slide]

The contraindications that have been listed in
your draft template include the ones with the bullets and in
bold: Cephalopelvic disproportion; face or other non-vertex
presentation; extreme prematurity; fetal coagulopathies;
recent fetal scalp sampling. The other, smaller
contraindications we chose not to list but certainly would
appreciate a discussion of them if you feel it is
appropriate to bring it back into the guidance: Intact
membranes; delivery that requires excessive traction;
operator inexperience; inability to achieve proper
application; and scalp damage.

[Slide]

The next section in the labeling guidance is
warnings. These are all the warnings that are listed in the
guidance. What I wanted to bring out for you are the areas
that are underlined. I hope you can see that underlining in
the slide.
Specifically, the first point recommends that we limit the use of the vacuum device to individuals with experience in the use of vacuum extractors.

The second point is that we have recommended a total of ten minutes of accrued time for the vacuum to be on during the delivery attempt.

The third is that we have made a comment, and it is the fifth bullet, never to exceed XXX mmHg. This is in part dependent on the manufacturer. However, if the panel feels that there is an absolute pressure that the vacuum should not exceed, that should certainly be incorporated into the guidance.

Finally the last bullet, we have recommended that the device should be discontinued if it has popped off three times.

[Slide]

I will just apply the same to the precautions. I am not going to discuss them all in their entirety, although, you know, we welcome comments on any and all of the points. Particularly, rocking motions and torque have been pointed out as being dangerous. The last precaution, the post-delivery precaution recommends that the neonatal unit be advised of all vacuum deliveries.

[Slide]

The fetal adverse events--and attempt was made to
list these in the order of severity, the most severe being the first. Unfortunately, whenever you are listing adverse events you have to recognize that the level of severity can also be an important factor, not only the injury itself but how severe it is and, again, we welcome any comments or reorganization of either of those two lists.

[Slide]

Patient counseling information is not always a standard in the current fetal vacuum extraction labeling. We have included the following: The physician should consider the following point in counseling the patient about this device: As time permits, the patient should be apprised of the risks associated with vacuum delivery in relation to the risks of not using the device in the individual circumstance.

[Slide]

This is sub-section one of the clinician use information. What we found in specifically looking at the literature and the ACOG Technical Bulletin of 1994 is that not only were there indications and contraindications, but there were what has been termed prerequisites to vacuum assisted delivery, in other words, circumstances surrounding the hospital, the patient or the operator that are necessary in order to conduct a safe and effective trial of fetal vacuum extraction.
I will read these for you. Again, this is a draft list and we welcome and encourage discussion. Knowledge of the mechanism of labor by the operator; knowledge of the actual course of labor of the patient who requires vacuum assisted delivery; know as precisely as possible the station, position and attitude of the fetal head; engaged fetal head; no demonstrable clinical cephalopelvic disproportion.

[Slide]

Empty bladder; term or near term infant; adequate anesthesia; experienced operator of supervisor; willingness to abandon the procedure; capability to perform a cesarean section; and neonatal resuscitation expertise be available.

[Slide]

The last four overheads are devoted to the proper application of the fetal vacuum extractor. Here, at the FDA, we recognize that we cannot in its entirety explain how to put on a vacuum and how to use it in this. Also, we recognize that different cups will have slightly varying ways to do this.

However, we wanted to give an idea of how this labeling should be done, and that is the function of a guidance. The preparation section reinforces the idea that the exact knowledge of the fetal position is critical. Conduct a vaginal examination to confirm the degree of
dilation and effacement of the cervix. The condition of the membranes, the presentation and position with reference to the size and shape of the birth canal.

[Slide]

The directions for use placement for fetal head--we chose the recommendations for placement from the ACOG Technical Bulletin from 1994. The center of the cup should be over the sagittal suture and about 3 cm in front of the posterior fontanelle.

[Slide]

Again, I would just like to point out specific points in assisting with delivery and discontinuation of the device, and those are underlined. We have recommended that the vacuum extractor always be used in synchronization with the contraction. Again, a discussion of the maximum amount of vacuum that should be applied. Then, a recommendation that if the cup starts to come off, hold the edge of the cup in close contact with the head to avoid loss of the vacuum.

There was discussion as to whether we should recommend a number of pulls that you should attempt with a vacuum extractor before you discontinued. The decision that we made in dealing with this particular number, because numbers are sometimes difficult to determine, is to use this statement instead.

[Slide]
If descent does not accompany each contraction and pull with the vacuum on, it is advisable to discontinue the procedure.

I do hope that we have created a labeling template that will provide good ground for discussion and move us along further in developing the final guidance. I look forward to the discussion. Thank you.

Open Committee Discussion

DR. BLANCO: Thank you very much Dr. Mitchell. At this time, we are actually running a little ahead of schedule, but we are doing so well I think if the panel members so desire we can go ahead and continue, and begin the discussion rather than taking a break, and if the discussion gets long we can always take a break during a part of it. Do I see agreement? Agreement is made. So, therefore, we are going to go ahead and begin the open committee discussion.

I think that at this point, if we go ahead and get Dr. Mitchell back, she can lead us with the specific questions that the FDA would like for the panel to discuss.

DR. ROY: While we are waiting, could we just have a point of information? We have percentages of operative deliveries that we have heard, but we haven't heard how many deliveries are there in the U.S.

DR. BLANCO: Use the mike, please. Please wait
until you get to the microphone.

DR. MARINAC-DABIC: The total number of deliveries was four million, a little bit more than 4,100,000 deliveries in the United States in 1995, and the total number of deliveries in which vacuum extraction was used was a little bit more than 228,000.

DR. ROY: Thank you.

DR. MARINAC-DABIC: You are welcome. Shall I stay here for other questions?

DR. BLANCO: No, we are fine. We will go ahead with Dr. Mitchell to address the specific questions.

DR. MITCHELL: CDRH recently issued a public health advisory on fetal vacuum extractors for vacuum assisted delivery. One element of the advisory was clinical management advice that vacuum assisted delivery should only be performed for recognized clinical indications. FDA staff has prepared the draft labeling guidance in a template format so that manufacturers can apply it to their own individual devices. The panel is being asked to comment on the draft guidance labeling template.

Dr. Blanco, how would you like me to go through the questions?

DR. BLANCO: Read the first question in its totality and then we will go ahead and start discussing it, and we will use your overheads which I think will help us in
the discussion.

DR. MITCHELL: Question one, indications for use:

(a) Please comment individually on each listed indication:
Prolonged second stage labor; non-reassuring fetal heart rate
pattern; maternal medical illness that prohibits adequate
second state labor; placental abruption; cord prolapse.

(b) Historically, the literature gives a number
of indications that are subsets of each of these
indications. Manufacturers have used this literature to
include these subsets in their labeling. Should these be
classified as unique indications for use, or mentioned as
appropriate in the warnings and precautions?

(c) How should other potential indications not
listed, such as cesarean section and borderline
cephalopelvic disproportion, be addressed?

DR. BLANCO: Thank you. First of all, I would
like to go ahead and begin the discussion by reminding
everyone, the panel and the public, that we are looking at
regulation of an instrument and not determining medical
practice. FDA is not in the business of determining medical
practice. So, keep that in mind as we go through some of
the later questions.

I thought what we might do is actually use Dr.
Mitchell's slides because there is more detail in her slides
concerning the actual subset under each of these listed
indications, plus, you do have them in your folder but can we bring in the more detailed ones, please? The one that has the subset?

So, the first indication in question 1(a) is commenting on prolonged second stage labor, which has been subdivided actually into three sections, maternal, fetal and maternal-fetal. We have up there the maternal indications. Any panel member want to begin the discussion? Dr. Chatman?

DR. CHATMAN: I would just like a point of information, a definition of prolonged second stage. Is that two hours? Four hours, or nine hours, or what?

DR. BLANCO: Well, how would you like to see the panel recommend to the FDA that they define it, number one, and number two, is it defined within the subset of information that they have placed up there for us to look at, in your estimation?

DR. CHATMAN: I think maternal exhaustion can occur within ten minutes and, you know, I don't see those as being definitions.

DR. BLANCO: How would you like to see them then?

DR. CHATMAN: That was the question that I asked.

[Laughter]

DR. BLANCO: I am turning it right back to you. I don't have the answers. I mean, do we want to make it a time limit or do we want to say in the judgment--you know,
essentially, should this instrument be utilized if you have
maternal exhaustion at 30 minutes, or do you want to make
them wait two hours because you are going to define
prolonged second stage as two hours? Dr. Allen, what do you
think?

DR. ALLEN: Well, you know, we are not deciding
medical care and I think definitions of prolonged second
stage have been well documented for nullips and multips.
So, just looking at these maternal indications, maternal
exhaustion, lack of cooperation may not have a time limit on
it. So, that is one point. Excessive analgesia, do you
wait until you get to two hours for a multip or three hours
for a primip before you decide that the analgesia is
excessive?

DR. BLANCO: Or you wait until the analgesia wears
off?

DR. ALLEN: Right.

DR. BLANCO: I mean, is that an indication?

DR. ALLEN: I am going on, and I think the last
two items under maternal--inadequate contraction activity
leading to failure to descent and rotate really lends itself
to a strict definition, or this is what you are looking at
in explaining your prolonged second stage, as well as
uterine inertia. These are all definitions of dysfunctional
second stage, those last two items. So, those are clear-
I think the more ambiguous items are the first three, and I think we need to decide, if we want to decide if they are indications in and of themselves, and are there other ways of addressing this rather than putting a vacuum on. As you said, with excessive analgesia, do you just let the epidural wear off? Do you decrease it?

My opinion, I think the first two don't really need a time limit. I don't know if you want to go round the room on that one, those first two.

DR. BLANCO: Go ahead. Why don't you finish and then we will let other folks tackle it. We will do the maternals all together first.

DR. ALLEN: Okay, and just to follow your suggestion with the third--I think the first two would not require a time definition. You can have an exhausted mother and you can evaluate that and decide that without waiting your full two or three hours, or four hours for an O.P., and for lack of cooperation there is a need to fall under prolonged second stage once you are in second stage.

Excessive analgesia can be treated appropriately by modulating your dose. The last two definitely fall under prolonged second state. That has been the diagnosis of the prolonged, the underlying etiology.

DR. BLANCO: So, essentially, if I read you
correctly, your suggestion is not to put a time limit since
some of these wouldn't be improved with a time limit
necessarily, namely, the first, second and the fourth and
fifth. Then, the question is whether for excessive
analgesia that is even a significant one that we ought to
include in there. Does that summarize it? Anyone else have
any opinions? Dr. Mitchell would like to say something.

DR. MITCHELL: I just want to clarify--I am not
sure if it is a clarification; maybe it is for me. Our
intention in the labeling template, which is the guidance
document that we have, is that the only indication that is
listed in there is prolonged second stage labor. So, if any
of those indications--we felt all the other indications were
sort of subcategories of that prolonged second stage of
labor. If you don't feel that that term, prolonged second
stage labor, adequately defines these, or that some of these
need to be identified as separate categories and placed into
the indications in the guidance, that is the information
that we need to know. Is that helpful?

DR. BLANCO: Yes, it is very helpful. I think if
you are looking at it that way--I mean, I know maternal
exhaustion is certainly an indication to try to intervene,
but if you told me maternal exhaustion and expected me to
figure that that was defined as prolonged second stage, I
would never have gotten it. So, I am not sure that it fits
as a definition of it.

I think I would be more supportive, while trying
to be more inclusive, of really defining and using the sub-
definitions as part of the guidance document rather than
just using the general terms because prolonged second stage,
as Dr. Chatman brought up, is a very well defined term that
means X amount of time if you are nulliparous or X amount of
time if you are a multipara and, so, if you just lock it
into that you have really not included actually any of those
in there, I would say. So, I think—and I am seeing some
heads shaking, yes, on the panel. So I think the panel
would rather see the expanded examples and definitions
included, rather than just the overall headings. Am I
reading the panel right? Subir, what do you think?

DR. ROY: I am a gynecologist, but my recollection
of obstetrics was that labor, or lack of prolonged second
stage was, in the presence of adequate contractions, not
having progress. If we are operating with that sort of
general definition, then certainly maternal exhaustion, lack
of cooperation, excessive analgesia, uterine inertia all fit
that. The fourth one is the simple definition of what
happens when you have inadequate contractions. So, it seems
to me almost redundant.

MS. YOUNG: Could I comment? I think we have some
real problems with the terms that are up there as being
subgroups. There has always been professional disagreement about what dystocia is and what it is not. It has been called sort of an umbrella term. I mean, NIH years ago tried to grapple with what dystocia was. You know, to see it up there under fetal indications as opposed to maternal indications—certainly, definitions of dystocia could be called maternal indications. So, I think it is going to be extremely difficult to deal with that unless this group and the FDA comes to a decision about what a definition of dystocia is. As I say, professional groups, NIH, everybody else, individual practitioners, can't decide what dystocia is and what it is not.

DR. SHARTS-HOPKO: I think as a category title, rather than prolonged second stage labor, which connotes the time limits that are well promulgated, maybe you simply want to call it failure of the second stage labor to progress.

DR. BLANCO: I think, you know, that might be a suggested terminology. I guess my issue, as still a practicing obstetrician at times, I know that vacuum has been used, and probably appropriately, for some of the subsets there, and I guess I would not have considered them to have been necessarily because I had a prolonged second stage or maybe a failure. I guess I would disagree with Subir. You may have someone who is exhausted and has progressed in the second stage, and you may want to
terminate that delivery if it is a low and inappropriate presentation. You know, if we say failure of the second stage of labor, that may not fit in there if we are trying to be purists about it. Dr. Chatman?

DR. CHATMAN: Just to muddy the waters a little bit more, you know, a prolonged second stage could be a contraindication to the use of vacuum because of the attendant morbidity that has been reported in that scenario. So, it could be that this terminology is very difficult to apply in this circumstance.

DR. BLANCO: Okay, having said that it is difficult to apply, I think the FDA would still like some guidance on what are some things that are indications. Dr. Allen?

DR. ALLEN: Well, I think using good clinical judgment, you could say in and of itself prolonged second stage, after the appropriate evaluation, would be an indication for the usage of vacuum extraction, after you take into account the contraindications and after you do your assessment of the presenting part, station, position, etc.

I am just wondering if you want to pull out as a separate indication maternal exhaustion, and pull out as a separate indication lack of cooperation, and not put them under prolonged second stage.
DR. BLANCO: Well, I will tell you what I think we need to do. I think we need to come up with what we think the indications are and they can divvy it up and put it in an outline or whatever form they want, and what we ought to say is are these things for which a vacuum procedure reasonably might be done and work as an indication. I think from what everyone has said, the one thing they have agreed is about the only one that had any controversy was the excessive analgesia; that all the others no one would have a problem with a vacuum extraction as an indication. Is that correct? Go ahead, Dr. Chatman.

DR. CHATMAN: Dr. Mitchell, was that excessive analgesia meant to specifically target patients that had epidurals? Am I misreading that?

DR. MITCHELL: That was taken directly out of some indications from an approved device, and that is as specific as it was. So, I would assume so but I can't--yes, I would assume so.

DR. BLANCO: What do you think, Don? Should it be included in there? If it is an epidural, should it just be allowed to wear off?

DR. CHATMAN: I know in practice vacuum is used in patients who have had epidurals because they don't push in the second stage.

DR. BLANCO: Okay. So, you would go for leaving
DR. CHATMAN: All things being equal, sure.

DR. BLANCO: All right. How about fetal? I think Miss Young brings up a good point. I am not sure what dystocia is over on the fetal side. If anything, maternal-fetal or maternal.

MS. YOUNG: And, in fact, uterine inertia has been also classified, you know, under the umbrella term of dystocia.

DR. BLANCO: Right.

DR. ROY: Heart rate tracing is more fetal indication.

DR. BLANCO: Right, heart rate tracing is next.

DR. ROY: But that is what I am saying. I would agree with what has been said about why these, other than occiput posterior presentation perhaps, what that dystocia business is there for.

DR. BLANCO: Dr. Mitchell, would you like to expound on how dystocia made its way up here?

[Laughter]

DR. MITCHELL: Again, these are the indications that have been taken from a combination of the literature and the previously approved fetal vacuum extractors. I mean, all I can tell you is that I looked up dystocia in a medical dictionary and the definition was "difficult birth."
DR. BLANCO: Huh, that helps!

[Laughter]

Well, I would think in looking at what we might be thinking of here, I think the issue is really what I would call an arrest of descent. If you had someone who does not descend, whether it be because of lack of flexion couples with malposition in the absence of CPD, or if you had someone who fails to descend—and, again, I think we will bring this up when we look at indications and contraindications. I think one of the things we need to address is the fact that high vacuums and mid vacuums may carry the same morbidity and mortality as high forceps or mid forceps, but we need to look at whether those are inappropriate ways of using it. So, I don’t imply failure to descend at a very high station but just failure to descend when all the other findings are appropriate. I would change that to failure to descent or arrest of descent rather than dystocia because, again, I agree, I am not sure what the term dystocia by itself means. Would that be acceptable, Miss Young?

MS. YOUNG: Yes.

DR. ALLEN: Do you want that under fetal?

DR. BLANCO: I wouldn’t put it under fetal. I would put it under maternal; maternal-fetal. Again, dystocia due to lack of flexion—I would probably take the
word dystocia out and say arrested descent due to lack of flexion. I think that is really what we mean and that probably, again, doesn't belong under fetal but probably under maternal or maternal-fetal.

Then occiput posterior, as stated, would mean if you just had an occiput posterior. I think in reality it is probably again arrested descent with an occiput posterior maybe, or should it just be if you have an occiput posterior presentation and you are down far enough, that is an indication in and of itself for a vacuum?

MS. YOUNG: Can I ask a question? In terms of the occiput posterior presentation, can't sometimes just a simple change in the mother's position change that? So, if I assume that a change in the maternal position can, in fact, change the presentation, then I have concerns about it sort of being up there in terms of somebody immediately saying there is an occiput posterior presentation; okay, let's put her on the vacuum.

DR. BLANCO: You worded what I mean to say much better than I did. That is the point I was trying to make. Is occiput posterior in and of itself in a fetus that is descending appropriately an indication to do a vacuum extraction? I didn't make it clear but that is exactly the point I was trying to make. Dr. Roy?

DR. ROY: In and of itself, I don't think it is a
reason. We are only indicating it in its presence and with
inappropriate or insufficient labor. Then it would be an
indication but not in an of itself.

DR. BLANCO: What do you all think?

DR. CHATMAN: I would agree with that. There are
other strategies for managing occiput posterior too.

Perhaps those should be taken into consideration as well,
not only lack of descent but failure of other strategies to
convert an occiput posterior to an anterior.

DR. BLANCO: All right. So, occiput posterior by
itself is probably not an indication, and occiput posterior
with failure of other attempts at correction or arrested
descent. Are you comfortable with that, Dr. Allen?

DR. ALLEN: Yes.

DR. BLANCO: Then maternal and fetal failure to
deliver spontaneously following an appropriately managed
second stage--that is awfully general. That seems very
general. You could include almost anything under that. Do
you want to leave it when a statement is that general, or is
everybody happy with that? That might almost take care of
everything else. That may be the first one.

DR. CHATMAN: Do we need some clarification on
what that really means?

DR. BLANCO: I suspect it has probably gotten out
of prior indications that someone put. No, I don’t think we
need to make her come up every time to tell us that.

Yes, I think it is fairly general statement. It is probably appropriate because it gives physicians an ability to make a medical judgment, which is what we want. We don't want to interfere with medical judgment; we want to regulate the device. The reality is you want to do something if you have a failure to deliver and you have appropriately managed second stage. So, maybe it should go at the top as a major indication. That looks like a consensus. So, we can move on. Anything else? Anything that we want to add in terms of prolonged second stage?

Anything that might fit under here? No takers?

All right, next is non-reassuring fetal heart rate pattern that Dr. Roy brought up. Since you brought it up, why don't you make some comments on these, Subir?

DR. ROY: You are trying to make an obstetrician out of me.

DR. BLANCO: Why not?

DR. ROY: Well, I think obstetricians will make judgments according to however the fetal distress comes about. The distinction will be whether the labor has progressed sufficiently to facilitate prompt delivery with an operative outlet delivery versus a cesarean section. So, a non-reassuring fetal heart rate pattern that can be addressed quickly and promptly with outlet delivery,
DR. CHATMAN: I was just wondering, I think the non-reassuring fetal heart rate pattern is there in order to avoid fetal distress, and we have fetal distress in here twice and I think it might be a good idea to use other terminology.

DR. BLANCO: See, I think in this one, quite the opposite of what I said before, I would go for just the non-reassuring fetal heart rate and not the specifics because we are essentially repeating. I mean, does it really matter? Whether you call it fetal distress or fetal compromise, which I like better, does it matter if it is evidenced by this, by that, or whatever? If you call it a fetal compromise you have a reason to intervene.

DR. CHATMAN: Well, just because the fetal heart rate is abnormal doesn't mean the fetus is compromised.

DR. BLANCO: Right.

DR. CHATMAN: You have to do a lot more to find out that the fetus is compromised, I would think, than just look at a strip.

DR. BLANCO: So you would want it more refined. You would want it as fetal compromise as opposed to a non-reassuring fetal heart rate pattern? Is that where you are going?

DR. CHATMAN: No, what I was saying was that we
havent determined that the baby is compromised. We know the fetal heart rate is abnormal but we don't know that the baby is compromised in many situations.

DR. BLANCO: Right.

DR. CHATMAN: So, for that reason, acute fetal distress--I am not sure that has--I mean, how do we determine the baby is in acute distress?

DR. BLANCO: Well, I don't think it is our role. Remember, we are regulating a medical device; we are not practicing medicine. So, I think the issue is we have to make it a guideline that is some indication but the judgment of what fits into that guideline, to some extent, is a medical judgment by the trained individual that is about to use this device.

DR. CHATMAN: Okay, well, I am just raising an objection to the terminology fetal distress.

DR. BLANCO: But I am not sure which way you want us to go. That is what I am trying to get from you. I mean, do you want to drop fetal distress and say fetal compromise, or non-reassuring fetal heart tracing is enough, knowing that you may intervene in a subset of fetuses that didn't need it because they are not compromised enough that they needed immediate intervention? That is what I am trying to get out. Do we want to say evidence of fetal compromise should be the big heading, or is non-reassuring
fetal heart rate tracing good enough as the big heading?

DR. CHATMAN: For me, the latter.

DR. BLANCO: Fetal compromise--

DR. CHATMAN: No--

DR. BLANCO: Non-reassuring. I can't figure out which is the former and which is the latter. I have to learn English.

MS. YOUNG: For me, the latter as well because actually the recent literature and I think standards--this has been just within the last year or so--have really come down hard on the term fetal distress as just not being definitive enough and now wanting, in fact, to get rid of the term fetal distress and replace it with something else, the something else being non-reassuring fetal heart rate pattern.

DR. ROY: Is it just that or is it a not-correctable fetal heart pattern. It is the not-correctable one that you have to make a judgment about delivery. Can we still use the word "late deceleration," or is that out of vogue, too?

DR. BLANCO: No; that is not out of vogue. I have the same problem but I don't know that I would fix it, necessarily, but using lates because I think, again, you are going into the judgment of the physician interpreting the fetal heart-rate strip and making a decision on is this baby
in trouble that needs to be delivered now or have I got more
time.

Let's say you have a non-reactive non-stress test
and you may even have a few late decelerations. And you go
to induce that patient. That is a non-reassuring fetal
heart-rate pattern and that would give you enough of an
indication right then and there to do a vacuum delivery.
You may not be anywhere where you need to do that, but you
have already got that.

I think we need to go beyond a non-reassuring
definition to something where--I don't like fetal distress
either--but something to where it is not-correctable or the
fetus is in trouble enough that it needs some intervention
as opposed to allowing labor to continue for the vacuum to
be used.

Does that make any sense?

DR. ROY: Yes; if it is non-correctable, you need
delivery and the fetus is down far enough to be delivered by
outlet, operative delivery, then you go to vacuum. If it is
not, if it is up too high, then you go to Caesarian section.

DR. BLANCO: Does that give you all enough
guidance on that one? Anything else anyone else wants to
say about this one?

DR. ALLEN: Can we take out the specific
etiologies like IUGR and oligohydramnios and cord
compression? I don't think--

DR. BLANCO: I think we threw all five of those out. I think that was the consensus that it is better to make some term, as Dr. Roy said--do you want to say it again?

DR. ROY: No.

DR. BLANCO: We will look at the transcript and get it, but, essentially some evidence of fetal compromise that is not correctable, requires prompt delivery and other indications for a vacuum and no contraindications for the vacuum exist. You will accept that paraphrase?

The next one is maternal medical illnesses that prohibit adequate second-stage labor, need to avoid voluntary expulsive efforts, medical illnesses that mandate shortening of the second stage of labor and sudden maternal compromise.

DR. ALLEN: I would just limit it to need to avoid voluntary expulsive efforts and sudden maternal compromise because the usual indications for shortening the second stage are those cardiopulmonary diseases that prohibit valsalva.

DR. BLANCO: Yes; and 2 and 3 seem, to me, to be the same thing. They seem to be just a restatement.

Anything else on this one? It seems fairly straightforward.

All right. We are progressing well. The next
one; placental abruption and cord prolapse. No pun intended on "progressing well." Placental abruption and cord prolapse. What do you all think about those?

DR. CHATMAN: They are bad things.

DR. BLANCO: Not good; right. Let's not have any of them happen.

DR. ALLEN: I was just wondering where you put the cord in the cup?

DR. BLANCO: Not in the cup; no, I don't think so. Not in the cup. Let's take them one at a time. Let's separate them because they are different entities. I should not have joined them. Placental abruption; let's do that one first. Is that an indication, in and of itself, for a vacuum extraction.

DR. ALLEN: Do we have to say the degree of separation?

DR. BLANCO: What is important? I guess the way I would look at it, what is important in an abruption that is going to make you want to intervene quickly. I would think it would be fetal compromise. I think that we have already covered it that that may be an entity where it may be used but I think it has already been covered.

If you have got a stable placental abruption, a mother who is progressing in labor, do you really need to intervene? Is that an indication to intervene?
DR. CHATMAN: It could be acute and progressing. If you can make a diagnosis of abruption and the baby is still okay and she is completely dilated and a plus 2, why wait?

DR. BLANCO: So you would leave it in?

DR. CHATMAN: I think so.

DR. BLANCO: Any other comments from the panel? There is a lot of shuffling in the audience. Before we shut all the discussion off, we will have another little public session so you can be writing these down if you want to make some comments on some of the things we are saying.

So leave placental abruption in as an indication for that intervention that you mentioned. I would probably want to see fetal compromise but I am willing to let it go, try to be more inclusive.

What about cord prolapse? I guess the issue here, and I don't have any experience, actually, doing a vacuum on a cord prolapse and I have done a lot of vacuums. So I don't know whether that would really be something where I would be troubled that you are going to get some problems from the cord when you try to deliver the baby with a vacuum.

Give your opinion, Dr. Allen.

DR. ALLEN: It just seems to me when we have had a cord prolapse, we have pushed the head up and delivered
abdominally. Since I have never been in this situation where I have had a cord prolapse with full dilatation at plus-2 or plus-3 station--usually, as you say, the cord prolapse is before the cervix is fully dilated.

DR. ROY: The floating head, unengaged and all the rest of it. So, yes; it is sort of a strange scenario. How would that happen?

DR. CHATMAN: An occult cord prolapse.

DR. BLANCO: But how would you make the diagnosis in occult? You would probably make it by something we have already covered which is some evidence of fetal decompensation. So you would have the indication of fetal decompensation rather than cord prolapse.

DR. CHATMAN: We should just eliminate these two, then. It would be just fine with me.

DR. BLANCO: All right.

DR. ALLEN: My vote would be to eliminate both of these.

DR. BLANCO: Both of these?

DR. ALLEN: Yes.

DR. BLANCO: Anybody feel strongly--

DR. CHATMAN: They would be a very narrow, narrow, narrow indications in these situations.

DR. BLANCO: And they are likely to fit under one of the other criteria that we have already agreed to. So we
are not happy with abruption or cord prolapses as indications.

    Now we go into part (b). Historically, the literature gives a number of indications that are a subset of each of these indications. Manufacturers have used this literature to include these subsets in their labeling. Should these be classified as unique indications for use or mentioned as appropriate in the warnings or precautions?

    I don't think this is "others" yet. I think what they are talking about here in this question--and Dr. Mitchell, please address this if I am incorrect or correct--is the subset that we have already discussed. We sort of did (a) and (b) together. We have done (a) and (b) together. We think some of them need to be dropped, some of them need to be put in as major indications and some are okay as just suggestions within the larger categories.

    So let's go on, then, to (c) and that is what you had up there. It is, how should other potential indications not listed--Caesarian section, borderline CPD, et cetera, be addressed. Specifically C-section, borderline CPD, incompletely dilated cervix, mid- or high-pelvis extraction, elective and unengaged fetal head. I guess I feel strongly enough about a couple of these that I am going to make the comments.

    I am very concerned about incompletely dilated
cervix, high pelvic extraction and elective use and
unengaged head, which is—that is high-high. That is really
high. I think those are problematic for me to include them
as indications. I think we ought to treat the instrument
essentially similar to forceps. I would have some problems
with those.

DR. ROY: I also had a problem with--someone cited
statistics, 5 to 7 percent of vacuum use is at the time of
Caesarian section. That was news to me. I had never even
considered it. Why would you need to do vacuum at the time
of C section?

DR. BLANCO: I think the reason given was for,
like, an elective C-section with a floating head where you
may not want to push on the uterus and elevate the head--I
would be interested to see some data. Again, it is not a
use and it may be my own lack of information on data of its
use in that way.

Does the FDA have some readily available data on
the use of the vacuum in this manner?

DR. YIN: No; we don't. Most likely, we did a lot
of literature search. And so we don't have exact data.

DR. ROY: Dr. Gilstrap, I think, mentioned that
the ACOG position was directly in opposition to that. Did I
phrase the ACOG position on that, the use of vacuum at the
time of C-section?
DR. HARVEY: Dr. Gilstrap, please come up to the mike. Thanks.

DR. GILSTRAP: Again, the main point from ACOG just was there was no data on its efficacy and safety for use so that we wouldn't list it as a recommendation.

DR. BLANCO: Thank you.

Let's take a five-minute break.

[Break.]

DR. BLANCO: Since we are looking for some other information that other folks have and we have some people that can help us in our deliberations, we have asked both Dr. Diane Mitchell of the FDA to come join us in the panel and also Dr. Larry Gilstrap, whom you heard before as a representative of ACOG. We have asked him not to join the panel as a representative of ACOG, but to join the panel as a well-known, nationally known, writer on these sorts of areas as a well-known academician.

So we will go ahead and get started. We will have some time for public comment before we finish all of our discussions. So if you have some items, you will be able to do that.

I think Dr. Gilstrap has just a couple of things that he wants to bring up and then we will go on to this particular discussion.

DR. GILSTRAP: Just really quickly. I think on
the indications, a good easy way to handle this would be to put them under maternal indications and fetal indications, just two broad categories. Most of those would fit nicely.

With regard to the non-reassuring fetal heart-rate pattern, I certainly agree with the comments made. You don’t just bail out with one of those. But if you put persistent non-reassuring fetal heart-rate pattern, it would imply that you tried other things to try to make that go away. So if it was persistent and it didn’t go away after you tried all those things, then you could either do Caesarian, if it is up too high, or use the vacuum.

One last comment I made. Somebody--I can’t remember who made the comment that there hadn’t been any litigation with this or law suits. There has been definite litigation regarding vacuum.

DR. BLANCO: That was one particular company and they may have been referring to their particular product, just to make that clear.

Let’s now move on to 1(c). That is the other indications. I think let’s tackle the ones that most folks are pretty clear that they don’t think really should be included. And that would be the unengaged head, the high pelvic extraction, the incompletely dilated cervix and, possibly, the elective included in there.

MS. YOUNG: Can I add to that borderline CPD?
What is borderline CPD? If anyone can give me a definition of that--

DR. BLANCO: I was going to discuss that one so I am happy to include it in the ones that I don't really think represent an indication. If there is data, I would love to see it but I would be surprised if there is a set of data to support those as indications that would be extensive.

How does the rest of the panel feel?

DR. CHATMAN: I agree. The definition begs for some clarification and I can't see it is forthcoming.

DR. ALLEN: I agree. I think this would be a category that would set a first- or second-year resident up for a bad delivery.

DR. BLANCO: So we think those should not really be included. What about elective and Caesarian section. Shall we tackle each one of those independently? Let's try C-section first. Most of the panel didn't have a lot of experience or a lot of knowledge of its use at the time of Caesarian section. It has been listed as a classification in the current listings of some of the manufacturers, but no one seems to be aware of that data.

Larry, do you know of any data using it?

DR. GILSTRAP: No; I am not aware of any data. I know a lot of clinicians say they use it and I always ask them how do you get it on correctly at that time unless the
head is just presenting just perfectly for you to do that.

I don't know why they want to use it anyhow. I think until we have some data that it is safe that we ought to not list it as an indication.

DR. BLANCO: So I think that theoretically this could be a potential indication but the panel recommendation would be that the FDA review what data is available about its safety and efficacy at the time of Caesarian section before listing it as an indication. Is that fair enough for the panel?

DR. ALLEN: Yes.

DR. BLANCO: What about elective use? Ms. Young, come on.

MS. YOUNG: I have a problem with that.

DR. BLANCO: There is a elective use of forceps in certain very specific settings. Do we want to say that this can't be used? Dr. Allen?

DR. ALLEN: You can think of it the same way you can think of elective forceps, that you would like for someone to be well versed and familiar with the instrument prior to being in an emergent situation. So, perhaps, there is a teaching role for learning how to place this on the head at what station and what kind of traction forceps to use. That is the only time I can see using it electively is in instructing someone who is progressing nicely with a
nice unmolded head where the landmarks are easily palpated and just going through the motions.

Other than that, I can think of no other reason to use it electively.

DR. CHATMAN: If you use it in a patient who has an epidural, it is elective. If the patient is going to deliver vaginally, anyway. She is not exhausted. The fetus is fine. She's fine. She just doesn't have any pushing ability. If you use it in that situation, that is elective.

MS. SHARTS-HOPKO: We took care of that category, I thought.

DR. BLANCO: Yes. That is what I was trying to remember. I think we left the inability to push because of analgesia and that we left that in.

DR. GILSTRAP: I think if the panel decides to leave elective in it ought to at least say that it must be in an outlet position, just like for elective forceps. It is very clearly defined that elective forceps should never be done until the conditions for outlet delivery are met.

DR. BLANCO: Even though it is not one of the questions, I think that if the panel would agree, I think that the suggestion that this instrument, unless proven otherwise with further data, should be considered essentially similar to what we do with forceps. This is probably a very reasonable type of approach.
How does the panel feel about that as a recommendation to the FDA? Okay? So using the nomenclature that we use for forceps, et cetera, would be useful.

I guess that addresses those so let's move on to No. 2, contraindications to use. 2(a), please comment individually on each listed contraindication. Does anybody want to start tackling some of these?

MS. YOUNG: How are you going to determine cephalopelvic disproportion. Again, it is a term about which there is professional disagreement in terms of its definition.

DR. GILSTRAP: You could say "known" cephalopelvic disproportion so that if you had a woman who had had a fractured pelvis or something that was obviously known that she had known cephalopelvic disproportion. It sort of seems like such common sense. Otherwise, I would leave it out totally.

The other one I have a comment on is where you have extreme prematurity listed. I am not sure what the definition of extreme prematurity is because, under one of the prerequisites later on, it says term, or near term. So if we are going to use that as a prerequisite later on, to say term and near-term, then we can't have extreme prematurity.

DR. BLANCO: Would you put in just "prematurity?"
DR. GILSTRAP: Yes. I don't have a lot of data for this, but a lot of people say less than 32 weeks. I hate putting numbers and things on it.

DR. BLANCO: I would rather, unless we have hard data--I guess we could look at it two ways. One way would just be it is a contraindication which essentially means--and we learned this the other day--a contraindication means it shouldn't be used under any circumstances in this particular setting as opposed to a warning or a caution where, in certain circumstances, you may want to use it but you don't want to use it on just everybody.

In other words, if we can think of settings where we might have a 32-weeker that we might want to deliver very quickly and this would be the given method that we would want to do, we recognize there might be a risk in the preemie to applying the vacuum but we think the risk of not doing it is greater, then that really may be more of a warning or a caution.

Dr. Yin, I am seeing if you are agreeing with me in terms of regulatory language rather than a contraindication where a contraindication would really be something where there should be no time in which you would want to use it in that setting.

DR. GILSTRAP: Then it probably ought to stay that way, extreme. I agree.
DR. BLANCO: Stay with extreme maturity?

DR. GILSTRAP: Right.

DR. BLANCO: Would you ever want to do it? But we may want to add prematurity in a warning or a caution so that there is some thought given to whether you want to utilize it. What does the panel think? Reasonable?

That takes care of that one. What about face or other non-vertex presentations? Leave that as a contraindication? Yes? We will get to CPD. We are going to tackle that one last. Fetal coagulopathies and fetal scalp-blood sampling. Those are still contraindications, pretty straightforward.

DR. ROY: Point of information. What is the time frame after fetal scalp sampling that one could safely do this, or is it prohibited during the labor and delivery--

DR. NEUMANN: I was going to say the same thing; what is the definition of recent?

DR. BLANCO: There is not a recent up there. But the question is would, after a certain amount of time, it be allowable to do a vacuum after you have had fetal scalp sampling. Again, let's remember maybe this is one where we also need to look at the various levels of concern. If we put it here as a contraindication that means it should not, cannot, be used, should that be a warning rather than a contraindication, a warning you may not want to use it soon.
after a fetal scalp pH.

I have absolutely no idea how to define it.

Again, this is one of the things where we I think we are
trying to make reasonable decisions on theoretical issues
that make sense and that are common sense but where I think
data would be very, very helpful to have and to obtain.

DR. GILSTRAP: I think it would be better under,
maybe, a warning because if someone came out and had a flat
tracing, came in in labor, and you did a scalp blood sample
to see whether they were acidotic or not but then you didn’t
do another one for several hours, I don’t know why you
couldn’t use a vacuum.

DR. ROY: That is the reason, on the left-hand
side, they have got recent. That is what we were asking.

DR. BLANCO: The problem is, then, we need to
define what recent would be to give some guidance. I am not
sure that I know enough to let you know that.

DR. YIN: I think another thing, just to make this
broad enough, some people are looking, experimentally,
anyway, and I believe there are some products under
consideration of other devices put on the fetal scalp that
would penetrate the skin. I think we ought to include that
along with the scalp sampling as a contraindication.

DR. GILSTRAP: But I think it would be better
under a warning and not as an absolute contraindication
because, again, it is very unlikely that a baby is going to bleed to death from putting--that you are not going to see hemorrhage from--

DR. BLANCO: Yes; I think a contradiction and the issue to deal with time is something to the effect of any time the baby's skin has been broken during labor, caution should be exercised to insure that excessive bleeding does not occur during the application of the vacuum.

How's that? Is that reasonable? Does that kind of address it?

MS. SHARTS-HOPKO: The fetal coagulopathies; could we add the word "known," because I don't think you hang out and do a diagnostic workup.

DR. BLANCO: No. You are right. Let's go to CPD, go back to that one. Again, I recognize Ms. Young's concern over what that means. I think the issue here is you make the decision that you have a baby that is larger than the pelvis is going to be able to deliver, is the concept here, you don't want to try to do this.

How you make that diagnosis is certainly art and not science. Where shall we go with CPD? What is the panel's pleasure.

DR. CHATMAN: Maybe this ties into what I was thinking about as another contraindication. I don't know whether it is pertinent or not, but a known macrosomic
infant; are we going to be able to use a vacuum in that
circumstance? Then you get into the definition of what
macrosomic is, 4,000 or 4,500 grams and the size of the
pelvis and stuff like that.

I don't even know if that is an appropriate
inclusion but it would concern me, I guess.

DR. GILSTRAP: I think if you put "known or
suspected" cephalopelvic disproportion then that would take
care of, maybe, some of your concern if you thought you had
a 5,000-gram baby in there as opposed to, say, 4,500, would
there be so much argument over that definition. But a 5,000
or 5,500 gram baby or something like that where you
suspected there would be cephalopelvic disproportion or
shoulder dystocia.

DR. ALLEN: I think it should stay in because you
have earlier that you are using this for prolonged second
stage but, in your understanding of why your second stage is
prolonged, at the top of your differential is cephalopelvic
disproportion, you should not be putting the vacuum on, the
same way as you have had a dysfunctional first stage and
then a slow descent, and you have an estimated fetal weight
greater than 4,500 grams, you are loath to do anything
vaginally.

I think what we are looking to do is to prevent
these untoward events. I appreciate what you are saying
about putting in cautionary notes as opposed to absolute contraindications but I think this is significant. I think CPD is a significant contributor to bad events, that it should stay in.

DR. BLANCO: I don’t disagree. I think it should be a contraindication. What I was actually probably trying to arrive at is should we try to define it a little bit more in terms of saying something to the effect, "Baby larger than the pelvis," or an estimation of that.

But it looks like we want to leave it as CPD.

DR. ALLEN: I think it gets too complex trying to define CPD because there are so many different variations of it.

DR. BLANCO: CPD it is. It stays on there.

DR. CHATMAN: What about macrosomia.

DR. BLANCO: Let’s talk about macrosomia.

DR. CHATMAN: Is that not considered a--

DR. BLANCO: Macrosomia might fit in under CPD if you think the baby is too large for the pelvis. That is going to be your concern with a large baby. I don’t know if you specifically want to put it in.

DR. GILSTRAP: Why don’t we put "fetal pelvic disproportion."

MS. YOUNG: Yes; that would be better.

DR. BLANCO: That would be a better way and that
would include your macrosomia on that. That is an excellent suggestion. Excellent.

That takes care of the bold ones. Let’s talk about the ones in smaller print which are the next set on questions. That is 2(b). Intact membranes, delivery that requires excessive traction, operator inexperience, inability to achieve proper application and scalp damage.

MS. YOUNG: Can I have a go at experience? I would like to know what operator inexperience is and a definition of what operator experience is because if you go down to 4--I know it has been circled--we are talking about the vacuum delivery should be limited to those individuals with experience.

I don’t really know what that means. I don’t know who an experienced person is. Is that somebody who has done five vacuum extractions? Is it someone who has done it for twenty years, like our visitor from Australia. I don’t know. What is "experienced" here?

DR. GILSTRAP: I would like to leave it, too, under the warning part because you could have an inexperienced operator but a very experienced teacher.

DR. BLANCO: I think maybe not here but I think somewhere it is experienced operator or supervisor. I guess that is in the other one. So maybe what we need to do is add that to this part, someone without experience in vacuum...
You have brought up a point that hospitals wrestle with in terms of staff privileging and privileging for procedures. I don't think that we can get into that. I think what we need to regulate is we need to say there should be a level of experience that residents should be being taught, that physicians who are going to use this instrument need to have.

I don't know that we can set that standard, but there needs to be some level. It shouldn't be that, "I have never done one and I am going to do one," and someone is doing that. But I don't know how we can define that.

I have been at meetings where you wrestle with that and you don't get very far. Any comments on that?

DR. CHATMAN: We can't define it. That is credentialing, again, something we were talking about yesterday. We don't have the capacity to do anything.

DR. BLANCO: I think we need to regulate the instrument. That means the person needs to be familiar--maybe we can put it this way; maybe the operator needs to be familiar with the use of the equipment, or have a supervisor who is familiar with the use of the equipment.

You are no happier with that?

MS. YOUNG: No. I am throwing it out because I
see it as being an impossibility, really, to define.
Experience needs to involve, actually, not experience with
the equipment with experience with using the equipment—that
is, doing the procedure. I think that that needs to be
incorporated in the wording.

DR. BLANCO: Any other comments on the experience
issue for supervision? To me, the rest seemed pretty
straightforward. I think I would have put in bold letters,
not in little letters. But intact membranes, inability to
apply the cup, scalp damage or the requirement of excessive
traction are pretty much things that you shouldn't be doing
in trying to use this instrument.

Anyone feel differently?

DR. GILSTRAP: Pretty straightforward.

DR. BLANCO: I would put them in big, bold
letters, not little letters.

That takes care of 2. Anything else anyone wants
to say on 2?

3; the draft labeling template also addresses
warnings, precautions, adverse events, patient counseling
information and clinical-use information. Please comment on
each of these sections. If we could please put those
sections up. Who wants to start with some comments?

DR. MITCHELL: Dr. Blanco, before we get started,
just to point out, question 4 is asking to deal specifically
with the prerequisite section of clinician use, if you want to separate that out later.

DR. BLANCO: Okay.

DR. NEUMANN: Let me just begin the comments with a couple of questions about the numbers. The XXX, I think, is fine, but the ten minutes--I am curious where that came from and, since we have had several comments before about there being a lack of data, I think one of the things that we need to do is to determine what knowledge is missing and then, when the knowledge is missing, if we are coming up with numbers such as this, we ought to indicate that these are just rough estimates based on whatever they are based on and, hopefully, encourage more definitive definitions of these studies.

DR. ALLEN: Actually, there is a review article by Plauche which is talking about--I think it was this one. It was a prospective study that we read where there were about 300 deliveries in both arms, the control and the vacuum. In the vacuum-assisted arm--and both had pretty good results, comparable results. The accrued time was 20 minutes. So I was wondering where the ten minutes came from.

DR. BLANCO: Dr. Mitchell, do you want to address that?

DR. MITCHELL: There is no particular magic about ten minutes. Again, we looked at the information that we
had available to us which included the things that we have approved previously in the literature and the number--ten minutes was mentioned. Twenty minutes has also been said. This number is up for discussion.

DR. ALLEN: Actually, it is a the Bofill article, the randomized prospective trial of obstetric forceps versus the M-cup vacuum extractor with good results with the vacuum extractor and it was twenty-minute accrued time.

DR. BLANCO: Let me change the question around a little bit. Are we, maybe, trying to say here that we want to make sure that the operator doesn’t keep the vacuum on at high volume for the entire time waiting in between contractions or do we know if there is a magical time of having the vacuum on at high pressure that we need to react to.

My problem with this would be, having been in a labor and delivery unit, you are going to pump these things up, you are going to try and bring the head down and say--it comes down, but you didn’t quite accomplish the delivery. So you are going to lower it while the patient is not having a contraction, then you are going to pump it back up.

Pretty soon, it is going to be very difficult for you to tell how much time you have had the vacuum up and how much you have had it long. Again, I hate to make some arbitrary cutoff if we don’t really have some hard data to
show that we have got a worse outcome afterwards because I think, otherwise, we are practicing a little medicine and maybe practicing a little medical-legal medicine with doing this.

So I think the concept is the delivery should be accomplished within a reasonable amount of time. The vacuum should not be maintained at high vacuum except while the contraction is and traction is being applied and should be lowered to a lower level.

I am just throwing this out, guys. Give me your opinion—-to a lower level in between contractions and maybe word it more that way.

DR. GILSTRAP: I think it is somewhat confusing because it says the vacuum to remain at a maximum level. That implies that you keep it pumped up. And then it says "accrued" which implies that it is what you said, trying to add up the minutes. So I think that the whole deal here is that somewhere around, probably, fifteen minutes, you ought to have effected a delivery or go on to something else.

DR. BLANCO: Dr. Allen, do they use 20? Do have that number in that? Could you find that?

DR. ALLEN: Actually, now I am back to Plauche.

DR. BLANCO: If we are going to pick a number, let's hope we have some data to back it up.

DR. ALLEN: This is actually 1979, in June. They
had, in the summary and conclusions, they had some edematous scalp lesions which were unavoidable, abrasive and ecchymotic lesions can be reduced by keeping the negative suction to a maximum of 0.7 kilograms per centimeter squared, shortening the time of cup application to a maximum of 20 minutes and avoiding pulloffs of the suction cup.

Our experience indicates that a large vacuum-extractor cup induces fewer superficial scalp lacerations.

So this is an article written in 1979.

DR. BLANCO: What does that panel want to do? Do they want to fix a time? 15 minutes? 20 minutes?

DR. ALLEN: I really think it is clinical judgment. If the cup pops off three consecutive times and if you have a effected no descent--but if you are getting descent and you have a good application, I don’t know if there should be an absolute cutoff at the end of which you should have had a vaginal delivery.

I think if the cup keeps coming off, the application is poor. If there is no descent, then after maybe two or three pulls, maybe the number of pulls, and evaluate whether you have any descent or not.

DR. CHATMAN: Do we have any information to suggest that ten minutes of accrued time is dangerous, twenty minutes of accrued time is dangerous, thirty minutes of accrued time is dangerous? We don’t really have the
right to make a statement about accrued time. We don't have any information.

DR. BLANCO: Why don't we word it this way. If we are going to put in accrued time, we should look to see that it is compatible and supported by data and this would be the recommendation to the FDA.

DR. CHATMAN: I think that is good.

DR. BLANCO: If not, I think we need to use something in terms of expeditious or within a reasonable time.

DR. CHATMAN: Yes; a reasonable time.

DR. GILSTRAP: I would say, they are not allowed in maximum for a protracted period of time without progress and descent. If you are sitting there, obviously, for ten minutes and you are not budging--

DR. BLANCO: In some, it may be ten minutes because they don't budge, or five minutes and, in others, in fifteen, you can get the baby delivered.

DR. GILSTRAP: Because we don't do that with forceps or anything else. We don't say number of pulls or how long you can pull. But if you are not coming in that length of time--

DR. NEUMANN: I would just like to remind the FDA of some basis physics, that we can't consider any of these factors individually because they are all related. The
amount of pressure alone is not sufficient because you have to consider the surface area of which the pressure is applied to get the net force. The net force is related to the traction force that is applied.

The other issue that I think is important is the cup, itself, and the shape of the cup and the actual portion of the cup that comes in contact with the fetal head. All of these things interact and all of these things will have an effect on the numbers. Again, because there is no data, I think we have to limit ourselves to clinical good judgement. But that, of course, is very difficult to define numerically.

DR. ALLEN: The magic number of twenty minutes comes from the protocol in the Bofill article. But they do not give a rationale for that.

DR. BLANCO: I think they probably have some opinions. I think I would concur with Dr. Neumann, especially on the next one, the XXX. Each individual instrument may actually have some slightly different vacuum settings that it may require, depending on how the instrument, how the device is made.

I think the other issue that you made earlier, but I want to reiterate again, was that, probably if the determination of some of these numbers such as how high or how low to lower the pressure are more empiric than some
statement to that effect and how it was decided it should be arrived at so that is well documented.

The other thing is what about the three popoffs. Again, we are talking about something which is empiric but do we need three to know that we are not going to get this baby down? I usually don't let the residents go to three.

DR. GILSTRAP: A lot of people use two, just empirically. It is kind of hard to find hard, firm data. Plus, you might use more than three if you had an intern doing it and it wasn't on properly so it came off for that reason.

If it pops off, I would say, after proper application, then it is significant.

DR. BLANCO: My rationale has just been, well, if it popped off once, maybe I didn't get it right the first time. I will make sure I can do it right the second time. If it comes off the second time, it is telling me that I am not going to get that baby down, I would think.

Again, we are pulling numbers out of a hat. I don't think we have got data to show--and I guess the important thing would be can we obtain data and should we monitor the number of popoffs to see whether there is a relationship between--and this is a suggestion--whether there is a relationship between the cup popping off and the rate of adverse events.
DR. GILSTRAP: The way it is touted by manufacturer and in the literature is that the reason it is safe is it pops off if the baby is too big and the pelvis is too small. So that is the way it is touted.

DR. BLANCO: It would still be an interesting variable? Any other number that people want to suggest as a possibility? Any other comments on these particular warnings?

DR. ROY: Haven't we said something about individuals with experience or in the presence of people with experience.

DR. BLANCO: So either individuals with experience or supervised by an individual with experience. Somebody does have to teach somebody how to use the device.

DR. CHATMAN: There is a duplication here; never apply the cup of the device to any portion of the infant's face. We have also said that that is a contraindication to use it elsewhere. That shouldn't be a warning, anyway.

That should be a contraindication.

DR. KATZ: What was our conclusion on the number of popoffs?

DR. BLANCO: There wasn't one. I suggested two. They have three. I have put my rationale. Dr. Chatman has six. He likes the number 6. Do we want to make a conclusion, address that?
DR. KATZ: It is a matter of relevance but it is a matter for which there is no unique answer; right?

DR. BLANCO: Right.

DR. KATZ: I think something needs to be said. Is it judgment?

DR. BLANCO: In the lack of data, judgment might be the better part because, as Dr. Gilstrap points out, I look at popoffs as, well, does that increase my morbidity but yet it is touted as the good thing, that you can’t get into trouble with this because it will come off before, if the baby is not going to come out.

So, to some extent, some people view it as a good thing that it comes off. So it could be a judgment issue.

DR. KATZ: Does one know that it has been properly placed because, if we can state that the user knows that it has been properly placed, then we can qualify popoffs after proper placement.

DR. GILSTRAP: I think if you add it "after proper application." If you don’t know, you probably ought not to be using it. If you know that you put it on and it meets and there is no gap on the cup and you have it the proper distance and it comes off three times, you probably ought to quit.

DR. ALLEN: I don’t even know if you need to put a time frame on that. If, after proper application, the cup
pops off, then reassessment of the utility of this instrument is in order.

DR. CHATMAN: Who would admit to non-proper application?

DR. BLANCO: Lots of people.

DR. ALLEN: Oh; I think we all would, especially with a molded head.

DR. CHATMAN: Really, what Dr. Gilstrap says is true. If it is properly applied, you don’t need three times to tell it is not going to work. You don’t need that. But, then, I don’t think we ought to put a number in here, anyway.

DR. BLANCO: So it should be, "if, after proper application, there is not descent or progression in the delivery, the use of this instrument should be reevaluated or reassessed," something like that?

Everybody’s happy with that? Everybody’s got the warnings down? Shall we move on to precautions? Let’s take the precautions in labor. Any problem with any of those?

DR. GILSTRAP: I would say, "Always pull in synchronization with contractions or patient’s expulsory efforts or pushing," either/or.

DR. BLANCO: The other ones seem pretty straightforward. Any problems with those? Move on?

Post-delivery precautions. Should the neonatal
nursery be advised? Yes. We probably don't do it enough.

    MS. YOUNG: Can I add to that. I think that
maternal education is extremely important here. In this
country, as you know, with early discharge, the babies and
mothers have gone home within a very short period of time.
We haven't addressed the issue of antenatal education with a
pregnant woman on this particular issue but I think that
post-delivery precautions are very important as far as the
mother is concerned.

    She should be given information about symptoms in
her infant to watch for if this procedure was done on her,
or done on her baby.

    DR. BLANCO: I think that is a good suggestion.
Something has been pointed out to me on this one. If it
says, "Never use rocking movement, never apply torque,"
again, here, we are talking about the three levels. The
contraindication is an absolute issue. The warning is
something where you are allowing some judgment. And the
precautions are really something to be careful but that you
might do.

    So if we are really saying "never" to those two,
should we not move those up either into the warning or into
the contraindication category. If not, should we, instead,
say not "never," but say, "Do not use rocking movements. Do
not apply torque."
I'll tell you, I never was taught to do either one and never had even considered doing either one.

DR. GILSTRAP: I can't think of when you would use this maneuver. It is not like an asynclitic head where you rock it to make the head become synclitic with forceps and a sliding blade. So it is not the same principle.

DR. CHATMAN: What is a rocking motion?

DR. BLANCO: I guess it would be going back and forth in some direction. That is a good way to pop the cup off. I guess the issue, again, here is do we have data that that worsens the outcome? I would think, torque; why would you ever want to do torque? Is it to rotate a little bit? I guess. I don't know.

What level do we want to put these at?

DR. MITCHELL: These were issues that were specifically addressed with regards to the metal Malmstrom cup. That is where these two particular comments came from.

DR. BLANCO: So it may not be quite as applicable to the soft cups now in use? What is the panel's pleasure? Shall we leave them as precautions with this wording? Should we soften the wording?

DR. GILSTRAP: Again, I would agree with you, put "not" using rocking in labor instead of "never."

DR. ROY: Not or never makes not difference from the clinical point of view. That is an absolute statement.
DR. ALLEN: We can bring it up to the maternal soft tissue; do not involve any maternal soft tissue. I think maternal soft tissue in the cup should be an absolute contraindication.

DR. BLANCO: So then you would move the maternal soft tissue up to contraindications. I think I would probably agree with that. I would agree with that. I think these--I don't know. I would probably change the "never" and maybe move them up to warnings rather than precautions. They carry a little bit more weight to them.

DR. GILSTRAP: That is a good place for them.

DR. ALLEN: I think these were brought up because of the subgalean hematomas where you've had ripping of the vessels and the veins and these were, perhaps, the motions that, along with increased pressures, increased negative pressures, increased force, some shearing effects. My thinking this was put in to avoid any maneuver that would create a shearing of the vessels.

DR. BLANCO: Would you want to put them in contraindications?

DR. ALLEN: I would.

DR. GILSTRAP: I think that is an excellent point because you are supposed to pull with a perpendicular plane and not rock or use torque. So I agree. That is a good point.
DR. BLANCO: Anybody have a problem with moving them up to contraindications? It doesn't seem so so we would suggest that they get moved up.

I think that covers the precautions in labor. We talked about the post-delivery already. We think the neonatal unit should definitely be notified by we also think the mother should be given some education as to what to look for in case there is complication. That is probably a very good idea because, with a short stay in the hospital, some of these complications may not develop until they have left the hospital.

That takes care of precautions. Adverse effects is next. I don't have anything to add and I suspect that their review of the literature is probably better than my memory on what are going to be adverse effects from this procedure. So the list looks all right to me.

Larry, did you have a comment?

DR. GILSTRAP: I am just struggling with shoulder dystocia because shoulder dystocia is a result of vaginal delivery of which the vast majority can't be prevented or predicted. If we list this as an adverse effect of vacuum we are sort of saying if you don't use a vacuum, we could have prevented it. So I guess I am struggling with that one.

DR. BLANCO: The other way to look at it is the
shoulder dystocia--I guess there are two ways. You could say, "Well, if you didn't use the vacuum, you may not have delivered vaginally and you wouldn't have gotten the shoulder." But, at the same time, is the shoulder really related as a complication of the vacuum or is it a complication of the fact that you have got too big a baby or it is not presenting to the pelvis appropriate.

DR. GILSTRAP: But even in a small baby with a shoulder, you can get shoulder dystocia. Subgaleal hemorrhage, intracranial hemorrhage, retinal hemorrhage, they are all definite adverse effects of it, as are bruising and scalp injury. Those are all known effects. But I would just like to leave out shoulder dystocia.

DR. CHATMAN: What about neonatal jaundice and elevated bilirubin? Is that associated with the vacuum?

DR. GILSTRAP: Yes; it is well documented in the literature.

DR. ROY: And what about infection?

DR. GILSTRAP: That is another good point. I don't even see that.

DR. BLANCO: I didn't pick on that but I am not sure that this causes infection.

DR. GILSTRAP: Me either. That is a good point.

MS. YOUNG: Yes; I wondered where that came from.

DR. MITCHELL: That was in relation to a scalp
injury. A scalp injury could then develop infection. That is how that came about.

DR. BLANCO: We have got scalp injury.

DR. GILSTRAP: It is already covered; right.

DR. BLANCO: That is sort of a secondary event. The scalp injury is what the vacuum might do and then it might get infected or it might not. And that may be influenced by the care the neonate receives afterwards not so much the procedure, itself. You may want to have some statement about the shoulder but not that it is a direct adverse effect but that, in patients where—something to the effect that patients who have instrumented deliveries may have a higher rate of shoulder dystocia so you should be aware—or maybe just more like a notice and awareness that you may have a higher rate of shoulder dystocia in patients who had an instrumented vaginal delivery.

Don't you think that might be fair, Larry?

DR. GILSTRAP: Yes, especially if you are using it for—you keep bringing up the prolonged second stage which is a good point because those two together does increase the risk. But vacuum, in and of itself, is not noted to cause shoulder dystocia. But it does cause bruising and hemorrhage and a variety of other things.

DR. BLANCO: Anything else on any of these—

DR. GILSTRAP: Still fetal, or both?
DR. BLANCO: Whichever. Shall we move over to maternal?

DR. GILSTRAP: Maternal; I think, just leave hemorrhage. Get rid of uterine atony. I don't know that there is any evidence that operative vaginal delivery causes uterine atony. If you have hemorrhage, maybe that is from a laceration or a tear or whatever.

DR. BLANCO: Any other comments? Sounds like we dealt with those. What else do we have? Patient counseling information.

DR. CHATMAN: Does this mean there should be a permit?

DR. BLANCO: I'll tell you what. I would hate to have a permit in some of the settings I have been in when I wanted to do a vacuum? Do we require a permit to do forceps? We do to do a Caesarian, and some of them can be stat. At this point in someone's labor, how good an informed consent are you really going to get from a permit?

MS. YOUNG: I was going to sort of raise the issue of the timing of information. Would it not be appropriate for the woman, before she goes into labor, sometimes during her pregnancy, for her to be given some information about benefits and risks of this procedure along with benefits and risks of Caesarian section and other procedures as well.

I think the timing here--
DR. BLANCO: Let me tell you as I would see it. Again, this goes back to the regulatory issue of FDA; we are trying to regulate the device and make sure it is safe and effective. Essentially, if that gets put into the requirement, almost every woman, during her prenatal care, would need to have some education about the vacuum whether she ever has a vacuum or not.

The vacuum is still—it is only, what, 5.9 percent and everyone would have—how would you know who you were going to use it on before you get to the situation where you are going to use it?

MS. YOUNG: I realize that. When can the risks be—I think that we need to have—I guess I have a problem with "as time permits," because that is a sort of vague wording. Somebody could always say, "Yeah; well, there wasn’t enough time."

I would prefer to see that the patient be informed of the risks and just not put the proviso in there, "as time permits."

MS. SHARTS-HOPKO: Diony, you are in an emergent situation when this is going on. My observation is most of the time people say, "Look; this is what I need to do and this is why." But that is the time they had to say that.

DR. GILSTRAP: I think "as time permits" covers it because, as time permits, you might do it in a prenatal—in
your office. You may cover all those things if you want to. I cover those things. But, as you know, in certain patient populations that we have dealt with, you don't have time. They come in and they weren't seen prenatally.

You are not given that opportunity and then you discover they are bradycardic and the head is sitting there and you don't have time to go through all of that. So, "as time permits" does cover all of that. It is purposely vague and it is good.

MS. YOUNG: Too vague for me.

DR. BLANCO: Other members.

DR. ROY: I sort of like it. I have been persuaded that "as time permits" can really give you the flexibility to do the antepartum education if you choose to do it and have the occasion to do it. But, in advance of having to do it acutely, you explain to the patient in a few words what is going on and what needs to be done. You do it and you go with it.

MS. SHARTS-HOPKO: I also think good prenatal education covers that occurrence, forceps, Caesarian section, a trot through the NICU, those kinds of things.

MS. YOUNG: It should.

MS. SHARTS-HOPKO: Yes.

DR. BLANCO: But, again, I would point, I think in the overall population, it is about 8 percent. But, in
certain areas, like where he and I used to work, it is much higher than that and you are not going to be able to cover it prenatally.

MS. YOUNG: Just looking at that "as time permits," again, could one say something like "whenever possible," or, "in all possible situations," the patient should be apprised.

DR. GILSTRAP: But it is always possible. You could not effect the emergent delivery. You could take the time to go through all of that as the baby’s heart rate is down. "As time permits," I think, covers that better. If the baby is bradycardic and the heart rate is 70, you don’t have time to go through and say, "Here is what a subgaleal bleed is and a hematoma. Here is what this is. Here is what that is."

You have to say, "I need to get your baby out now. The quickest, best way I can is to use this instrument."

DR. BLANCO: I think Ms. Young’s objection is noted but I think the majority of the panel probably would like to see "as time permits."

Moving right along, as promised. Now we are really on No. 4 which is prerequisite information for a vacuum-assisted delivery. Actually, it is not exactly equivalent but I think it is probably additive. If it is redundant, some of it may be taken out but probably we need
to look at both.

Any comments?

DR. GILSTRAP: No. 3; I would just use the same
terminology and put "knowledge of the station, position and
attitude of the fetal head," as precisely as possible. The
American College uses that same terminology and I am trying
to get them to change it, also. Just to say "knowledge of
the station, position and attitude." Hopefully, it is the
best you can do anyhow. I don't know why we put that one
caveat in there in that part.

DR. BLANCO: Anything else? Again, here, we got
the no demonstrable CPD which I think we have said, three
different times in three different places. So I don't know
whether we need to have it everywhere. Maybe it is
important enough that it needs to be in more than one place.
But that is the other thing.

We did change it to fetal pelvic disproportion so
we probably ought to change it here as well if we are going
to leave it in here.

Any other problems with the five items on the
left? If not, let's proceed to the items on the right.
Engage fetal head; knowledge of the station, position and
attitude of the fetal head. Actually, Dr. Gilstrap, maybe
putting a proviso in there might be good because you say,
"knowledge of the station, position and attitude of the
fetal head," that means if you--say, you have a lot of
caput. Should you then not apply the vacuum because you are
not certain of where the occiput and where the sutures are?
I am just playing the devil’s advocate.

DR. GILSTRAP: I don’t think you ought to put it
on if you don’t know the exact position of the head. I
think that is where you get in trouble because if you have
so much caput and you put it on too far anteriorly, you get
extension of the head, that is a setup. That is a risk that
I don’t think you ought to be taking with a woman’s baby.

DR. BLANCO: So then it should specifically say,
"knowledge of the station, position and attitude of the
fetal head."

DR. GILSTRAP: You could be wrong. You could feel
a posterior fontanelle and think it is anterior. We have
all done that.

DR. BLANCO: Sure.

DR. GILSTRAP: I mean, to the best of your
knowledge of the head.

DR. BLANCO: I think the implication is--I think
that some people have said, "Well, vacuum is safe so even if
I don’t know exactly where the occiput is, if I get it close
by, I am going to be okay." I think what we are saying is,
"That is not good enough. We really do want you to put it
in the exact position."
DR. GILSTRAP: Absolutely.

DR. BLANCO: So we do want to know where that occiput is; right?

DR. GILSTRAP: Yes.

DR. BLANCO: Adequate anesthesia. I think we have already addressed the experienced operator or supervisor. Capability of performing a Caesarian section. Willingness to abandon the procedure. That might be a little general for folks. But I think it is necessary. You have got to be able to throw in the towel and say, "Okay; it is time to go another route."

I don't know if you want to word that any differently.

DR. GILSTRAP: I like it and I think it is very important. It is the same concept we had with forceps. This is not--you don't get a trophy for getting the baby out this way.

DR. BLANCO: So be it. Knowledge of the mechanism of labor by the operator. Knowledge of the actual course of labor or the patient who requires the vacuum-assisted delivery. Empty bladder. Term or near-term infant. No demonstrable clinical cephalopelvic disproportion. That is, I think, about the fifth time we have heard that one and we have changed it to fetal. And then, neonatal resuscitation expertise available.
MS. YOUNG: Can I ask a question about the last one, neonatal resuscitation. It occurred to me, what about a small community, rural hospital, where you have a family practitioner who is doing this delivery and is using this procedure. What does he or she need to have available in terms of neonatal resuscitation and what is the availability in terms of a small, rural hospital?

DR. GILSTRAP: Probably bag and mask. That is resuscitation.

MS. YOUNG: You are not talking about then.

DR. GILSTRAP: Someone that knows how to use a bag and a mask to ventilate a baby and not to do it too much. That is a relatively easy skill to teach. All of our midwives do that and our family-practice physicians do that.

DR. BLANCO: I think what Ms. Young is bringing up is even broader. It is the issue is there a community standard where some rural, small hospitals may have certain things available and not others or is there a national standard that, at your place, a high-powered institution, is going to be there.

I think, in this day and age, it is pretty much a community standard. The hospital has to meet standards or they shouldn’t be delivering babies, putting themselves in this position. But I think the neonatal resuscitation would
simply be someone with the ability to bag and mask the baby and provide oxygen, as Dr. Gilstrap says.

DR. GILSTRAP: Or we could say someone with "basic" instead of "advanced," where you have to be able to put a tube in.

MS. YOUNG: Okay.

DR. BLANCO: Any comments? Anybody?

MS. YOUNG: Is that any different from any other delivery? If you need neonatal resuscitation, you need neonatal resuscitation wherever they are delivered. Is it unique to those who are delivered by vacuum assistance?

DR. BLANCO: No; I think your point is well taken.

DR. CHATMAN: It can't be different in rural Iowa than it is in New York.

DR. BLANCO: I would hope not.

DR. GILSTRAP: That is a good point. Why don't we just leave it off. Good point. Excellent.

DR. BLANCO: Somebody brings up the point of home deliveries. I hope nobody--first of all, I don't even want to comment on home deliveries, but home deliveries with a vacuum extraction?

MS. YOUNG: No, no.

DR. BLANCO: I don't know about that.

MS. YOUNG: I am not aware that any have been done.
DR. BLANCO: Let's open up the meeting maybe for
about ten minutes or so, seven minutes or so, to the public.

DR. MITCHELL: I'm sorry; after prerequisites,
there is the directions for use.

DR. BLANCO: Oh; you mean I missed something here?

DR. MITCHELL: Persisting with delivery,
discontinuation of the delivery.

DR. BLANCO: I don't know if I am going to allow
you to slip that one by us, Dr. Mitchell. It is not on the
question here.

DR. MITCHELL: It was under the clinician use
information question.

DR. BLANCO: All right. Well, we will let you
slip it in, then. Here we go. Preparation, use of the
fetal vacuum extractor for assisted vaginal delivery and
placement under the fetal head.

DR. MITCHELL: That is only two of four overheads.

DR. BLANCO: Okay. Thank you for pointing that
out.

DR. ROY: Seems okay to me.

DR. BLANCO: The only thing I would say is that
one on the left is somewhat redundant of some of the things
we have already said in the second sentence. And the first
sentence may actually be somewhat device driven. Some of
the devices may be a little different. I think that may
also apply to the right.

So maybe what we can say is that, in general, they should have some description of the device-specific way in which it should be utilized and where it should be placed on the head. How does the panel feel about that? You can use this statement as a guide for the amount of information that needs to be provided. Okay? Any problem?

Let's move on. There is a fourth. Bring it on.

DR. MITCHELL: Again, I think the issues that I want to address specifically are underlined and then the first check mark on the second one.

DR. BLANCO: We would love to comment on all that you put before us, Dr. Mitchell.

DR. ALLEN: Again, with the pull and synchronization, I would put, "with the contraction or maternal expulsive efforts."

DR. BLANCO: And the XXX, again; that may be device specific. If not, some places should state how that level was arrived at.

DR. ALLEN: If the cup starts to come off--I don't know if we should encourage--if it is coming off for a reason, perhaps we should just let it come off rather than keeping the vacuum intact.

DR. BLANCO: What would you do, though, if you feel like it is going to come off? Would you rather stop
DR. ALLEN: Yes.

DR. BLANCO: But that is not just letting it come off. So maybe instead of saying what to do, you should say, "if it starts to come off, you should try to maintain it on, and recheck application."

DR. CHATMAN: If it starts to come off, reevaluate the--

DR. BLANCO: Yes; I think we need to add that because that is when you get a--usually, when you put it on and you feel all around, you make sure there is no maternal tissue, the way you get maternal tissue in is you pull on it and it starts to come off and you get a little maternal tissue in there. So I would add that, make sure there is no maternal tissue.

But how do you want it reworded, the second part of that sentence, or do you want to give some guidelines if it starts to come off?

DR. CHATMAN: Reevaluate the application?

DR. BLANCO: Okay; sounds fine. I think Dr. Gilstrap mentioned this when we were talking about--I don’t know if it was contraindications or warnings--if you don’t get descent, you probably better quit. You are not going to get a benefit out of the procedure. So I think that is important to put in there.
DR. ROY: Should that be highlighted in some way as opposed to the rest of the instructions?

DR. BLANCO: I think, again, as Dr. Gilstrap pointed out, you shouldn't feel like you are going to get a medal or a trophy for doing this to the point that you are going to get the patient to deliver vaginally. So it is probably an important concept.

Do we want to move it up? Remember the severity is contraindication, warnings, precautions and directions for use. Do we want to move it up in our concern list?

DR. MITCHELL: It is listed elsewhere.

DR. BLANCO: Is it?

DR. MITCHELL: Yes.

DR. BLANCO: At what level? Do you remember? As a warning--it is not a contraindication. So it must be a precaution or a warning; right?

DR. ALLEN: Yes.

DR. BLANCO: Is that okay with the panel?

MS. DOMECUS: You can also, in this section, just put a box around it, italicize it or bold it or something if you want it to stand out from the long list of directions for use.

DR. BLANCO: Okay.

DR. ROY: Italicize it or do something so that it jumps out at you.
MS. DOMECUS: Yes.

DR. BLANCO: Any other comments on any of this? Do you have anything else you would like for us to comment on, Dr. Mitchell?

DR. MITCHELL: Thank you very much. Those were the last two.

DR. BLANCO: Let's have a few moments of public discussion. Is there anyone in the public that would like to address this, address the panel, or address any issues? Please remember to identify yourself, your connection and conflict of interest.

MS. BILTZ: Tracy Biltz, Director of Medical Products with Prism Mityvac. I just wanted to, again, address our esteemed panel and all of the members here today to give you a little bit of background. That was a lot of discussion as to where did some of this information come from.

Clearly, as the originators of the product and as leaders in the marketplace, a lot of this stuff did come from our company. So let me just kind of give you some information as to how it got here.

First of all, I noted that it was difficult and, many times, challenging for us to define what is the definition of X, Y and Z. The reason that I believe that is because we are dealing with things that are normative
practice behavior standards versus evidence-based research prospective randomized studies.

What has evolved over the course of many years in the studies that we saw; as you saw the injuries ramping up, you all see usage of vacuum extraction ramping up. So you saw the converse happening with forceps. So there you see at least some explanation as to why you will see increased incidence. You have seen significantly larger uses of vacuum extractions especially in the teaching facilities.

There is actually a study by Dr. Bofill that cites the use of vacuum extraction being much greater in residents or physicians that were trained in the last ten years than those that were trained ten to twenty years ago.

I agree with most things that we stated here today. Just to give you at least some comment on, "Do not allow the vacuum to remain at maximum levels for ten minutes." Ten minutes is conservative. Obviously, we do have some attorneys that advise us. If you look in the research, you will see anything from ten to twenty minutes.

Dr. Bofill had twenty. That is accrued vacuum. Attorneys, obviously, are going to advise us, as a manufacturer, to be very conservative. So we chose ten minutes. And that is where that came from. So we would, obviously, and the clinicians would, prefer that that number be moved.
But that is not based on a prospective, randomized study. It is normative practice, accepted guidelines.

Additionally, with the three popoffs. Again, it is an arbitrary empirical number that has been designated, again not truly that has been researched.

Another point that I did want to raise that we didn’t discuss was underneath, on warnings and precautions, No. 4, there is a bullet point; vacuum pressure should be reduced between contractions.

DR. BLANCO: I’m sorry; let me interrupt you for a second--not what you are saying. Somebody is passing this along to have all the consultants’ addresses and E-mails. We can do that. Please go ahead. I’m sorry for the interruption.

MS. BILTZ: No problem. Vacuum pressure should be reduced between contractions to reduce the possibility of trauma to the neonatal scalp. There is a research study that was done by, again, Dr. Bofill. They had about 500 deliveries where they did not see any complications with the baby’s head and they left the vacuum intact throughout the procedure. They did not reduce the vacuum.

So there is at least a study that addresses that and we might want to look at that before we make this recommendation.

My only other comment and then I will allow
someone else to speak is that the primary reason I raised
the issue of Caesarian section is it is very much like some
of the things that we discussed today. Where did the ten
minutes accrue from, the three popoffs? Those things came
because our clinicians needed guidance and they wanted to
know what is happening across the nation and internationally
with the use of this product.

We can't go to evidence-based data but we need to
know what other clinicians are doing. That was from market
surveys and from information that we have gleaned over
twenty years of experience.

In the same regard, the use of vacuum extraction
with about 5 to 7 percent of Caesarian sections. That is,
again, from an analysis of how the product is being used and
that is primarily our job is to find out how it is being
used and then to try to determine how it should best be
used.

So I hope that at least that gives you some
information as to how this information has been developed.

Thank you.

DR. BLANCO: Thank you very much. We appreciate
your comments. Is there anyone else from the public or
industry that would like to make a comment?

DR. VACCA: I am Aldo Vacca. I am an obstetrician
from Brisbane in Australia. I would like to thank you for
the opportunity to speak and say how much I have enjoyed listening to the deliberations. I have one or two things I would like to comment on.

Firstly, no one has mentioned the Cochran Library database where there is the best available evidence for many of the questions that were raised here. I would suggest, if I may, that that is consulted and, particularly, the individual randomized controlled trials that were done there.

I was interested in Dr. Mitchell's paper that she didn't list as one of her recommendations, the training, because I think this is one of the crucial issues that needs to be addressed. I have some concern when we raised the issue of maternal exhaustion, lack of cooperation, excessive analgesia, inadequate contractions, and so on, as a major indication for vacuum extraction.

You must realize that you are running the risk of increasing the subgaleal hemorrhages because you are going to increase the traction force. My view would be, first of all, to increase--use other agents such as Pitocen to increase these and you will find--I have found that often the exhaustion is more psychological than physical.

I think we really should address those issues. It is a real worry. I think one needs to be very careful when we say maternal exhaustion because you run the risk of
increasing the injuries that you are trying to prevent.

I never, in the thirty years that I have been using the Malmstrom and then the Bird cups, the metal cups, I have never, ever reduced the pressure in between the contractions. I believe there is no evidence, whatsoever, and now we have got some randomized controlled evidence, that there is no benefit to be gained by doing this.

In fact, it may be distracting as we have commented on here. In my own hands and in my resident's I get concerned if there is one popoff. I do not, and I agree with Dr. Gilstrap, see that as a safety mechanism. There is a reason for popoff and, in my opinion, the vast majority can be prevented with correct technique.

I do think sudden popoffs are abrasive and, if we want to reduce many of the superficial scalp injuries then we should be preventing popoffs.

I would like to conclude in that I believe that every vacuum extraction should be audited. I do that in my unit. There should be feedback so that we know where we are going wrong. Many of the issues that were raised here would be addressed with proper auditing.

The final question I would like to raise is maternal counseling. I believe, as Dr. Young said, that there should be prenatal discussions about vacuum extraction. In my unit, we actually have the midwives
incorporating a prenatal discussion or format that I have produced. This is actually discussed in the prenatal classes.

I have produced a CD ROM in which case there is a section specifically devoted for the education and information of mothers and others. I dare say that many of us here are "others" as well. I have on the Internet an abridged version of this where people can access it for themselves.

I do believe there should be a general awareness of vacuum extraction for the people on whom we actually perform this instrumentation.

Once again, thank you for having me.

DR. BLANCO: Thank you for your comments. Any other public or industry comment? If not, Dr. Roy, did you want to make a comment?

DR. ROY: No. I just wanted to ask—he gave us his thirty years experience. How long do you leave the vacuum on?

DR. VACCA: I was pleased to hear that we concluded that there shouldn't be a time limit. I am answering your question in a roundabout fashion. Most vacuum extractions are completed within five to nine minutes. I would say that fifteen minutes is of no consequence.
It is not what happens while a cup is attached to the head. It is what you do afterwards. So I think there are traction forces and we heard about physics and so on before. I think there are more factors involved. Ten to fifteen minutes, I have no problem with that.

DR. BLANCO: Thank you. Dr. Yin or Mr. Pollard, would you like some parting comments from the FDA?

DR. YIN: Again, I want to thank the panel. This is really a very, very good serious discussion and we need it badly. I want to thank our Chairperson, again, Dr. Blanco. Every little thing is discussed. Nothing has been skipped. So I do thank you. I think we thank Dr. Gilstrap that is so willing to help us out and especially all the manufacturers.

Yes; we agree. We did use ACOG’s and all the companies to come up with this list. So it is very long. You know that we should not be blamed. Thank you all. Special thanks to the panel, the companies and our FDA staff. They worked very hard.

DR. BLANCO: Any comments, replies, from the panel members?

MS. YOUNG: May I just make a comment. I was going to do this before we went to the second open session on the template. I notice that only one reference is listed under No. 10 and that is an ACOG Technical Bulletin from
at

1 1994. I think that is inadequate as just one reference. I
2 think that there should be multiple references. They should
3 be as up to date as possible.

4 I agree very much with our Australian visitor that
5 the Cochran database should be investigated. I think in
6 studying any obstetric procedure or technology or practice,
7 one of the first lines of the literature search--and we have
8 to start doing it in this country. The other countries do
9 it; Australia, England, Europe. They look to the Cochran
10 collaboration, the Cochran database, as the gold standard in
11 terms of literature search.

12 We have been very slow in this country looking the
13 Cochran. So I can't underline that heavily enough.

14 DR. BLANCO: Thank you. Any other comments?
15 DR. GILSTRAP: I was just going to make one other
16 comment on one of the comments made in the public about
17 having a series of 500 consecutive babies without an injury
18 or a problem. Again, when we look at the frequency and
19 incidence of these injuries and fetal deaths, that certainly
20 doesn't rule out anything with that number.

21 DR. BLANCO: I want to thank Dr. Gilstrap for his
22 participation. It was very welcome and helped quite a bit.
23 I appreciate it. Dr. Mitchell and Marinac, thank you. I
24 want to thank all the panel members for a wonderful, very
25 educative and interesting two days. I thought it went well
and I want to thank all of the FDA staff for their wonderful support, Mr. Pollard, Dr. Yin, Dr. Harvey. Everyone else that presented and that was included did a great job. We appreciate it.

Thank you very much and, unless someone else has something else, we stand adjourned.

[Whereupon, at 4 o’clock p.m., the meeting was adjourned.]
CERTIFICATE

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