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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OBSTETRICS AND GYNECOLOGY DEVICES PANEL  
SIXTIETH MEETING

Volume II

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Rockville, Maryland

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1 Women's Hospital in Pensacola, Florida.

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

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

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

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

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

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

1 Gynecology Michael Reese Hospital in Chicago.

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

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

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

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

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

22 I would like to turn over the meeting now to Dr.  
23 Harvey, who will read some of the information. Before I do  
24 that, the FDA press contact this morning will be Dr. Yin,  
25 right at the end of the table.

1 DR. HARVEY: I would just like to read the  
2 conflict of interest statement for today's meeting.

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

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

23 We would like to note for the record that the  
24 agency took into consideration certain matters regarding Dr.  
25 Nancy Sharts-Hopko. This individual reported interests in

1 firms at issue, however, on matters not related to today's  
2 deliberations. Since these interests are not related to the  
3 specific issues before the panel, the agency has determined  
4 that she may participate.

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

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

15 I would also just like to point out that if you  
16 are interested in transcripts or videos of today's meeting,  
17 there are handouts at the sign-in area that you can take.

18 If there are any presenters to the panel who have  
19 not already been in touch with me, they should provide a  
20 hard copy of their remarks and overheads. Mr. Yung Pak, if  
21 you could stand up--you can provide those to him.

22 I would just like to note for the panel what their  
23 folder contents contain. You have an afternoon session as  
24 well. Your morning session materials are on the left side  
25 of the folder and your afternoon is on the right. Dr.

1 Blanco?

2 DR. BLANCO: Thank you, Dr. Harvey. At this time,  
3 it is our pleasure to introduce Mr. Colin Pollard. Mr.  
4 Pollard is the Chief of the Obstetrics and Gynecology  
5 Devices Branch, Center for Devices and Radiological Health,  
6 Rockville, Maryland. He will be making an introduction and  
7 general updates, and providing a brief overview of the  
8 purpose of this panel meeting.

9 **Introduction and General Updates**

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

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

21 In that context, we set up a variety of  
22 definitions for those kinds of studies, including the type  
23 of women to be studied. In this case it was premenopausal  
24 women; the diagnosis of abnormal uterine bleeding and the  
25 context of failed hormonal therapy; a scoring system and

1 quality of life indicators; and the time frames for studying  
2 that, including three months pretreatment and then the  
3 follow-up, six months, one year and up to three years.

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

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

21 Towards that point, the FDA staff has crafted a  
22 set of discussion questions that we are asking the panel to  
23 look at and give FDA comment back so that we can update our  
24 guidance document for this new indication. Dr. Diane  
25 Mitchell, the OB-GYN reviewer in our Branch, will be

1 presenting those questions to you but, before we do that, I  
2 think we are going to have the open public hearing first and  
3 after that Dr. Mitchell will introduce those discussion  
4 questions. Thank you.

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

11 [No response]

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

15 **Open Committee Discussion**

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

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

23 DR. MITCHELL: All right. Some postmenopausal  
24 women on hormone replacement therapy experience refractory  
25 troublesome uterine bleeding. Even after adequate hormone

1 replacement therapy management, some of these women still  
2 manifest such bleeding. Hormone replacement therapy is  
3 currently indicated for osteoporosis and vasomotor symptoms.

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

7 What constitutes refractory troublesome bleeding?  
8 Comment on bleeding patterns and durations.

9 What are other important indications for  
10 intervention?

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

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

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

20 Patient characteristics--should any of the  
21 following patient characteristics influence the inclusion or  
22 exclusion criteria for a clinical study of endometrial  
23 ablation for postmenopausal women on hormone replacement  
24 therapy? Specifically, age, perimenopausal status, dosage  
25 of estrogen, dosage and type of progesterone, uterine size,

1 history of successfully treated hyperplasia, risk factors  
2 for endometrial cancer such as obesity, smoking or  
3 associated conditions, and other.

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

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

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

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

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

1 the endometrial ablator.

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

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

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

25           So, yes, I think there is a subgroup of women who,

1 you know, will continue their hormone replacement therapy,  
2 and the argument is basically should those patients be  
3 offered this technology as a means of allowing them to  
4 continue their hormone replacement therapy, otherwise they  
5 are going to discontinue their therapy, which is probably  
6 not in their best interest.

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

21 DR. CHATMAN: I think that there is no question  
22 that there is a group of women, who are postmenopausal who  
23 have abnormal bleeding, who are suitable for this  
24 technology, and whether or not we like it, it is going to be  
25 applied. The question I think is, is it safe? Is it safe

1 because the uterus is atrophic, small, thin? Is it safe  
2 with reference to the issue of endometrial carcinoma  
3 becoming an occult disease in patients of this type, and  
4 being diagnosed late and, therefore, treated late and  
5 suboptimally?

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

17           MS. YOUNG: Well, I can't speak on the basis of  
18 studies, but my own experience and talking with other women  
19 in this age group that you are talking about, who could  
20 conceivably fall into the subgroup, I think that the first  
21 line of defense has to be manipulation of the hormone  
22 replacement therapy schedule. And, this is something that  
23 actually isn't done always by physicians. Some women I know  
24 have actually done their own investigations to look at a  
25 variety of schedules, and actually come across a schedule,

1 and I will mention the one which I sort of threw out to my  
2 own obstetrician-gynecologist which was five days on and two  
3 days off. And, it was very interesting that that particular  
4 schedule eliminated the bleeding.

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

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

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

1 [Laughter]

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

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

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

17 DR. CHATMAN: There is one very important  
18 difference, and that is maintaining hormone replacement  
19 therapy in these women. A lot of them will eliminate the  
20 medication to stop bleeding because they would rather not  
21 have the medication. There is no immediacy about taking the  
22 medication. So, a lot of patients that I know of in my own  
23 practice will stop taking hormone replacement therapy if the  
24 bleeding is not controlled. So, that is a big difference I  
25 think. What you are talking about is the totally elective

1 cosmetic procedure, and this is, I think, quite different  
2 because if we believe in hormone replacement therapy we are  
3 going to have to encourage patients to take it. This is one  
4 of the ways to do that.

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

19 DR. ROY: I am just having a little difficulty  
20 understanding why the FDA wishes to get involved in the  
21 algorithm as opposed to the device and its use, were there  
22 to be one, and how they would perhaps follow up. It seems  
23 to me that we are in the realm of the practice of medicine.  
24 As Miss Young mentioned, different practitioners practice it  
25 differently. Are we going to have a check list that says

1 that unless you have gone through the hoops that we hold out  
2 for you, you are not permitted to go forward?

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

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

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

22 [Laughter]

23 But if not, then we need to get to how do we  
24 identify that subset so that that subset can be identified  
25 and the companies can, you know, set up a study to utilize

1 it in that subset of patients. Dr. Chatman?

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

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

9 DR. CHATMAN: That is for all reasons?

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

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

15 DR. ROY: Well, there is a multiplicity of reasons  
16 and, you know, any excuse will do. If you have breast  
17 cancer, bleeding, tenderness, all these things sort of fall  
18 together somehow. I don't know that anyone has rigorously  
19 tried to characterize the specific reason why women  
20 discontinue but at least our clinical impression is that  
21 over fifty percent of those who discontinue do so because  
22 they either don't want to continue bleeding if they are on  
23 cyclic therapy, or they despise the unpredictability of the  
24 spotting and bleeding that occurs with combined continuous  
25 therapies.

1 DR. BLANCO: Let me try to bring the committee  
2 panel back to the question at hand. I think the first issue  
3 to address is the issue of is it a cosmetic procedure or is  
4 it something that medically can be offered? Okay? Because  
5 I think that is the crux. If we agree that there is a  
6 subset of patients where this may be of benefit either to  
7 stop the bleeding or to stop the bleeding so that they don't  
8 come off hormones, either way, then I think we need to  
9 define how we get to that subset. But I am hearing that  
10 some folks think that maybe it is not that important. What  
11 is the opinion of the panel?

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

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

21 DR. CHATMAN: I am not following that.

22 DR. BLANCO: Okay. Just basically, there is a  
23 subset of patients whom this might benefit, and the idea is  
24 who is that subset and what needs to be done to make sure  
25 they don't have safety issues, as you brought up--the

1 endometrial cancer issue, and how do we get to identify  
2 those patients. But there is a subset, and you would say  
3 any bleeding would be troublesome. That is what I think the  
4 committee is saying.

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

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

15 DR. ROY: I guess some people have pain. That is  
16 more associated with adenomyosis, and I think that is an  
17 important distinction. If there is pain associated with the  
18 bleeding, then perhaps other strategies could be  
19 entertained. McCausland, out at UC at Davis, recommended  
20 that prior to ablation a biopsy be taken, and if adenomyosis  
21 were present that ablation not be entertained because it  
22 wouldn't adequately treat that symptom complex. So, I don't  
23 know whether that is what they are referring to. That would  
24 be almost an exclusion, that if you found adenomyosis you  
25 wouldn't go ahead with attempting ablation.

1 DR. CHATMAN: It is unfortunate that you can't  
2 make a diagnosis of adenomyosis by simply biopsing the  
3 uterus. So, it is just not practical.

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

5 DR. CHATMAN: Yes.

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

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

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

18 DR. MITCHELL: Bleeding, of course, is the primary  
19 indication. The second question was just specifically if  
20 there was anything else of issue that should be entered into  
21 the decision-making, and I don't have anything specific,  
22 except to reinforce the idea that what we are looking at  
23 here is the risk-benefit ratio, and we want to make sure  
24 that for the patients who do receive endometrial ablation  
25 that the benefit of the procedure will outweigh the risk.

1 DR. BLANCO: All right, I think we can move on to  
2 (c) then. Go ahead.

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

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

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

23 Obviously, what we are looking at here, again, is  
24 not for the FDA to dictate medicine; what we are looking for  
25 is who would be a candidate for that subset of patients for

1 whom we said endometrial ablation might be useful, and what  
2 should the requirement be for hormone manipulation, if any,  
3 before they would be candidates? Anyone want to tackle  
4 that?

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

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

18 DR. SHIRK: Right.

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

23 DR. CHATMAN: I would say six.

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

1 [Laughter]

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

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

19 MR. POLLARD: I just wanted to make two comments,  
20 one with respect to the discussion that is going right now.  
21 We probably have to differentiate a little bit between what  
22 is an appropriate interventional approach to take here  
23 versus if you are going to do a clinical trial what kind of  
24 standardization should be made so that the information that  
25 you get at the end of the day has some kind of, you know,

1 predictability as to the effect of the device. I think that  
2 is some of the flavor of question 1(c).

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

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

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

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

21           DR. SHIRK: It seems to me that we really ought to  
22 answer question number two before we come back and answer  
23 (c) in number one because, I mean, basically the question is  
24 if you get a patient who is postmenopausal on HRT, basically  
25 how should you react to that, and after you have reacted to

1 that and worked the patient up appropriately and ruled out  
2 every other pathology that is causing it, then how would one  
3 proceed with hormone manipulation before the patient then  
4 becomes a candidate for endometrial ablation, which is, to  
5 me, the more logical approach to the problem?

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

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

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

18 DR. SHIRK: Okay. I think the big issue with  
19 work-up of patients in a postmenopausal range is that  
20 historically the OB-GYN and medical community in general has  
21 been programmed to ask one question, and that is does this  
22 patient have endometrial cancer or not. So, they basically  
23 ask only that question. They don't ask the question as to  
24 why is this patient bleeding. I would say that ninety  
25 percent of gynecologists who see a patient--and that

1 certainly would be substantiated in my practice because we  
2 did a big study on this in our practice a couple or three  
3 years ago--basically are just going to do an endometrial  
4 biopsy on this patient and say, "no, you don't have  
5 precancerous or cancerous lesions so let's start  
6 manipulating hormones," which doesn't really answer the  
7 question of why is this patient bleeding. So, the answer is  
8 that obviously endometrial biopsy is one of the important  
9 questions but doesn't answer the real question.

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

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

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

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

21 DR. BLANCO: Right.

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

24 DR. BLANCO: But it is part of that issue of, you  
25 know, before we would do an endometrial ablation we would

1 want to make sure that there are not polyps, submucosal  
2 myoma or something else that could be the reason for the  
3 bleeding that we know is a high percentage of the reason for  
4 the bleeding in this population.

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

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

16 DR. SHIRK: Right.

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

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

23 DR. BLANCO: So, saline infusion or hysteroscopy  
24 and endometrial biopsy to rule out carcinoma or precancerous  
25 lesion. Comments? Dr. Chatman, do you agree with that?

1 DR. CHATMAN: It sounds fine to me.

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

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

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

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

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

23 DR. CHATMAN: Well, I think it needs to be taken  
24 into consideration certainly because, evidently, it is a  
25 fairly significant factor in the development of endometrial

1 carcinoma in patients who have had ablations.

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

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

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

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

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

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

22 DR. SHIRK: I would think the big question is  
23 basically, you know, what constitutes medical risk for  
24 endometrial cancer in these patients. I guess if you go  
25 back to Sitiri and Bob McDonald's original article which

1 showed that high estrogen levels play a major role in  
2 developing endometrial cancer, back in 1970, basically when  
3 they looked at all the populations, basically obesity is the  
4 problem, not the diabetes and not the hypertension. It is  
5 basically the production of estrone peripherally, the high  
6 estrone levels that these patients have that is the high  
7 risk for endometrial cancer. So, I mean, it is pretty hard  
8 to start putting other medical diseases in as risk factors,  
9 I would think, I mean, unless you just want to lump obesity  
10 in as a factor.

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

23 DR. ROY: Right.

24 DR. BLANCO: I mean, it is just a matter that that  
25 needs to be followed to see whether it is detrimental or

1 beneficial even.

2 I guess the question that I was going to ask Dr.  
3 Chatman or anyone else is that we know that with an  
4 endometrial biopsy we don't sample a significant amount of  
5 the endometrial cavity. Okay? In patients that are at high  
6 risk before going to this procedure, like diabetics, should  
7 we do more than an endometrial biopsy, or should the  
8 requirement be the same? I don't know; I am just seeking  
9 opinions.

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

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

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

25 DR. ROY: But if you are going to use that are you

1 going to make a distinction that the endometrial echo  
2 complex be above a certain amount or be uniform, and if it  
3 is irregular then those individuals should have further  
4 evaluation?

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

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

17 DR. SHIRK: But the question is basically whatever  
18 we apply to the study would be applied criteria after the  
19 study to general use, and so obviously you then  
20 significantly limit general use by saying that all these  
21 patients have to be studied by hysteroscopy. In the future,  
22 essentially most of these patients are probably going to be  
23 studied by sonohysteroscopy. So, I still think it should be  
24 included in the study because that is in general how most of  
25 this is going to be handled when it is in general use.

1 DR. BLANCO: No, I don't think Dr. Roy was arguing  
2 that it shouldn't be included. I think what he was saying  
3 was that the whole point of hysteroscopy or saline infusion  
4 is to look to make sure that you don't have a situation  
5 where you are more than at high risk for an endometrial  
6 carcinoma or precancerous lesion but that you have enough  
7 suspicion that you want to do something else. Am I reading  
8 that right?

9 DR. ROY: Yes, that is right. I am actually  
10 asking for how you manage your patients. When you do the  
11 biopsy and they continue to bleed you do your vaginal-probe  
12 ultrasound with or without saline. I take it you are more  
13 inclined to do it with saline. But let's just suppose that  
14 you did the endometrial echo complex assessment and it was  
15 completely uniform, and you saw it well and it was less than  
16 5 mm. Would you then do sonohysteroscopy?

17 DR. SHIRK: No. But then the question is do you  
18 need a biopsy? If you have an endometrium certainly below  
19 3-4 mm or certainly 3 mm and you look at it, you can argue  
20 that you don't even need to do an endometrial biopsy. The  
21 incidence of endometrial carcinoma in those patients is so  
22 low that biopsy is no longer required.

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

24 DR. SHIRK: Well, but I mean that is the way the  
25 world is arguing right now, that if you do a

1 sonohysteroscopy and it is below 5 mm thickness, you don't  
2 even need to do an endometrial biopsy any more.

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

5 DR. SHIRK: Right.

6 DR. BLANCO: With saline?

7 DR. SHIRK: Not always.

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

10 DR. SHIRK: Right.

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

13 DR. SHIRK: Correct.

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

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

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

21 DR. SHIRK: Right.

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

25 [Laughter]

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

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

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

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

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

20           DR. CHATMAN: All pelvic exams are good exams.

21           DR. BLANCO: All right, I will go for that. All  
22 right, any other criteria? Anything else? Any other things  
23 that we need to look at? Should age make a difference?  
24 Dosage of the hormones that they are on? Types of hormones?  
25 No takers?

1 DR. CHATMAN: What about uterine size? I think  
2 the point Dr. Chatman made earlier is very, very important.  
3 This is a population, as opposed to the premenopausal where  
4 we haven't seen a lot of perforations in the data, where we  
5 may see that. You have smaller uteri, thinner uteri, and  
6 that may be a problem. So, I think particular attention  
7 needs to be paid to that.

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

9 DR. CHATMAN: That is right.

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

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

24 DR. NEUMANN: Yes. I think we will get to it in  
25 more detail in number four.

1 DR. BLANCO: Okay. Anything else about history of  
2 successfully treated hyperplasia? Would those patients be  
3 included in a study?

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

6 [Laughter]

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

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

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

25 DR. BLANCO: Right. We spoke a little bit about

1 risk for endometrial cancer already. Any other patient  
2 characteristics that you would deem important? No? Okay,  
3 let's move back to the tough one, 1(c). Does there need to  
4 be some hormonal manipulation prior to inclusion into the  
5 study?

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

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

18 MR. POLLARD: Yes, I just wanted to double check,  
19 before we move back to 1(c), on 2(b). We kind of moved  
20 right past the first four bullets and I just kind of wanted  
21 to remind the panel that this is probably the kind of study  
22 that is going to come back to the panel and you are going to  
23 be looking at it, and are there no basic constraints you  
24 want to place on a study of this sort with respect to age,  
25 perimenopausal status, and actually the third and fourth

1 bullets may kind of roll into your discussion of question  
2 1(c), but I just wanted to see. I mean, in terms of the  
3 kind of study that you would like to see at the end of the  
4 day, would you recommend some constraints in that regard?

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

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

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

17 DR. BLANCO: Right.

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

20 DR. BLANCO: And, the other issue that you are  
21 bringing up is that you don't really want perimenopausal.  
22 You want someone who is postmenopausal. For me, that was a  
23 given so I didn't even see why they put in the "peri."  
24 Isn't that kind of what you are saying as well?

25 DR. SHARTS-HOPKO: But you might want to exclude

1 the marked outliers with an age of, I don't know, 40 or 45  
2 to get out the 20s people.

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

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

13 DR. BLANCO: Dr. Sharts, okay? Anyone else?  
14 Okay, we have dealt with the younger. Is there a limit  
15 above which you don't think it should be used? I would  
16 think just the opposite. I mean, in some of the older women  
17 this may actually be a better procedure than trying to do  
18 some of the more interventional things that may end up  
19 happening.

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

24 DR. CHATMAN: And we should define it.

25 DR. BLANCO: Have at it.

1 DR. CHATMAN: Well, I don't know how to define  
2 that.

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

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

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

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

14 DR. BLANCO: Okay.

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

1 problems with their therapy. So, I don't think we are  
2 necessarily recommending that they go off therapy to assure  
3 that they are menopausal.

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

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

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

16 DR. BLANCO: Yes, I think it kind of defeats the  
17 purpose. I guess, at this point I would think probably  
18 leaving it general because, say, you have a fifty-seven year  
19 old who had a definite period of amenorrhea for three years  
20 before being put on replacement therapy, and maybe had an  
21 FSH back then that was markedly well elevated and well  
22 documented, to make that patient come off therapy now, you  
23 know, you will never get her in the study and you will  
24 probably never get her back in your office. So, I think it  
25 needs to be well thought out, and there needs to be some

1 certainty of the fact that they are postmenopausal, but  
2 maybe we will let FDA and the company wrestled with that one  
3 a little bit more. Is that all right? Can we move on?

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

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

22 DR. SHIRK: Well, in a preop work-up basically, I  
23 mean, anybody who is bleeding who is on just straight  
24 estrogen, I mean, I think they should have failed an  
25 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 DR. BLANCO: Well, I think the issue is more if  
14 you had someone who is totally on estrogen, and has not had  
15 any progesterone, our position that prior to being enrolled  
16 in the study the progesterone should be added and that may  
17 solve the problem and they are no longer candidates for the  
18 study. I think that is the issue they are looking at, and  
19 should there be some requirements. You would put in a  
20 requirement that people who have postmenopausal bleeding on  
21 estrogen alone are not candidates at that point; they need  
22 to be treated. They may need to be evaluated to see what  
23 their bleeding is, but they need to be treated with  
24 progesterone. So, patients who should be admitted to the  
25 study should be on estrogen-progesterone combination and

1 having bleeding on that.

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

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

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

23 DR. ROY: I think it comes down to if you are  
24 going to have the cohort of patients who are willing to  
25 consider going on any of these studies, the companies may

1 have to pay just to enroll many more patients because of all  
2 of these little caveats and differences in doses, and things  
3 like that, because if we insist that everybody fit into a  
4 specific slot it is, first of all, going to be difficult to  
5 do and, second of all, what are you going to extrapolate it  
6 to? So, I think the price that is going to have to be paid  
7 is studies that are of a much larger size.

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

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

25 DR. SHIRK: I think we have got some standard

1 answers over the long haul as to what the risk of developing  
2 endometrial cancer is in patients on estrogen-progesterone  
3 therapy. I don't think we have good answers on the  
4 alternative group of using estrogen alone.

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

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

22           DR. BLANCO: Well, let's take a step back because  
23 I think the issue we are trying to discuss is should we have  
24 a uniform hormonal therapy given to patients prior to  
25 inclusion into the study? Okay? In order to say that that

1 is important, we have to say the outcomes may be different  
2 if you don't set the study up that way. The complication of  
3 that is that, therefore, the indication is going to be that  
4 you have to go through that process each and every time.  
5 So, is there enough difference between individual types of  
6 estrogen and progesterone where you might think the outcome  
7 might be different, or is it just estrogen alone versus  
8 estrogen-progesterone combinations, and should they be  
9 differentiated? Or, should one of the two be excluded from  
10 the study? I think that is the question.

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

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

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

1 do that.

2 DR. BLANCO: Right.

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

11 DR. CHATMAN: That seems reasonable.

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

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

21 DR. ROY: Well, my sense would be--I just hate to  
22 interfere with physicians' and patients' management  
23 decisions. I mean, if they think they have gone as far as  
24 they are going to go and this is a legitimate alternative,  
25 then I think we should leave it up to them. If they want to

1 manipulate for a further period of time, then let them. But  
2 I think what is necessary is that all these steps be  
3 captured so that they can be looked at to see if it makes a  
4 difference ultimately.

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

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

1 in hormones, to some extent? So.

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

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

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

22 DR. ROY: I think it is real life and for some  
23 people one therapy may be all that the patient will accept  
24 or tolerate, or the physician wishes to undertake, where for  
25 someone else they will do everything possible to avoid any

1 sort of surgical manipulation, and they will go through five  
2 or six different groups. I think the key point is that the  
3 uniformity that we require to assess the suitability of  
4 acceptability of study results I think we have if we insist  
5 on a certain endometrial echo complex thickness, or below a  
6 certain amount regardless of whether it is one manipulation  
7 or five manipulations.

8 DR. BLANCO: All right. Any other comments on  
9 1(c) or any part of 2?

10 [No response]

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

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

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

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

24 DR. BLANCO: Yes, and I think also this procedure  
25 may not be that--I mean, there is a certain amount of size

1 that occupies the endometrium so it may not be all that  
2 useful.

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

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

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

25 DR. BLANCO: Right.

1 DR. ROY: I wouldn't want endometrial ablation  
2 under that circumstance.

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

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

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

8 DR. CHATMAN: But they use numbers.

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

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

18 [Brief recess]

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

23 MS. YOUNG: Yes, I would just like to bring up a  
24 couple of things specifically with regard to age and the  
25 other with regard to cosmetics.

1 I think that the postmenopausal woman actually  
2 falls within a very broad age range, and I think that it  
3 would be very difficult really to sort of give that age as  
4 sort of a beginning and an end. So, I really think that it  
5 is an individual matter that needs to be considered here.  
6 The patient's viewpoint in terms of how does this bleeding  
7 affect her life; how important is it to her. That is  
8 something that she needs to talk to her doctor about and the  
9 doctor needs to understand that there may be some  
10 psychological issues here and this, you know, brings up the  
11 matter that Dr. Shirk raised, which had to do with, you  
12 know, should this just be a cosmetic procedure. For some  
13 women it may be psychologically extremely important that a  
14 certain amount of bleeding is something beyond which she  
15 will not tolerate. Another woman might be able to tolerate  
16 a great deal more bleeding. So, I think it is something  
17 that has to be worked out with the physician, and those  
18 things need to be taken into consideration.

19 DR. BLANCO: Thank you. Dr. Roy?

20 DR. ROY: I think the other thing I don't believe  
21 the committee was saying needs to be clarified, and that is  
22 that when hormone replacement therapy is instituted, just  
23 like with birth control pills or in the postmenopause, there  
24 is an adjustment period, and the vast majority of  
25 atypicality to bleeding tends to go away with use. We are

1 not recommending that at the very outset, if you have some  
2 spotting or heavy bleeding, that you immediately capitulate.

3 I think it would be unlikely for clinicians or  
4 patients to just say that the majority would not fit into  
5 that categorically. I think what we are suggesting is that  
6 when there is a persistent problem that has been manipulated  
7 and has failed, and they go through the assessments and come  
8 out the other end with an endometrial echo complex that is  
9 below 5, or whatever, that is the cohort that would be  
10 candidates for this study.

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

18 DR. CHATMAN: Well, we can't have as an endpoint  
19 amenorrhea.

20 DR. BLANCO: We can or we cannot?

21 DR. CHATMAN: We cannot. I don't think that is  
22 practical.

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

25 DR. KATZ: I was just wondering how the answer to

1 this question relates to the questions we were discussing  
2 yesterday for premenopausal women, where we have these two  
3 different types of endpoints. Is there anything different  
4 about postmenopausal women in this regard? We certainly  
5 have that as a frame of reference.

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

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

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

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

25 DR. CHATMAN: Well, the control group is

1 menopausal women who are not on hormone replacement therapy.

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

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

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

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

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

22 DR. BLANCO: Any other comments?

23 [No response]

24 All right, what about secondary endpoints?  
25 Quality of life indicators? Mr. Pollard?

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

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

17 MR. POLLARD: The hormonal therapy, you mean?

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

1 assure amenorrhea.

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

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

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

22 DR. SHIRK: Then the question is you have to  
23 decide what your endpoint is going to be to decide what your  
24 control group is going to be, and, you know, is  
25 discontinuation more of a subjective finding than--what

1 objective endpoint can we find that will allow both a  
2 control group and a research group?

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

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

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

21 DR. BLANCO: Well, what would be the alternative  
22 in today's practice? What would be the alternative to  
23 ablation? I mean, what happens now if a woman comes in and  
24 she has postmenopausal bleeding. She gets evaluated; she  
25 doesn't have polyps; she doesn't have submucosal myoma; she

1 doesn't have endometrial carcinoma or any hyperplasia. I  
2 mean, what is the comparable option that she is likely to  
3 receive at that point? I mean, I think it is hormone  
4 change, change in the hormones. So, do people go into  
5 resection? Is that the other option? You mentioned  
6 surgery, Dr. Roy. Do you want to elaborate?

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

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

1 with it and, you know, is comfortable with that amount? Any  
2 comments?

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

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

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

14 DR. BLANCO: But the issue then becomes what is an  
15 acceptable level of women who either become amenorrheic or  
16 say their bleeding has decreased that you would say this is  
17 part of the armamentarium that should be used on these  
18 patients. Are you going to require 80 percent, 50 percent,  
19 20 percent?

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

24 DR. BLANCO: I am not sure I follow you. I think  
25 the control group would be women where you would need to

1 alter or manipulate the hormone treatment and then compare  
2 them because what is going to happen, okay, I have someone  
3 on estrogen-progesterone combination X at Y dose, and what I  
4 am going to do now is if she complains of bleeding, I am  
5 going to make sure she doesn't have hyperplasia, by whatever  
6 methods I want to do that, and then I am likely to change  
7 her to this other dose. Then I am going to treat her for X  
8 length of time, and at that point I am going to see is she  
9 amenorrheic; did I decrease the bleeding; you know, is she  
10 happy or at least accepting of the amount of bleeding? To  
11 me, it would seem that is what you would want to compare. I  
12 will stop there.

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

25 MS. DOMECUS: It seems to be difficult to set a

1 precise number, and maybe we can go back to Dr. Roy's  
2 suggestion about the patients remaining on hormone  
3 replacement therapy as a definition of success but then add  
4 into that all patients who discontinued but didn't do so for  
5 reasons related to their bleeding, and then I think the  
6 patient could serve as their own control if that was the  
7 definition of success.

8 DR. BLANCO: Well, I am troubled by that, and I  
9 will tell you what I am troubled by. That makes the  
10 assumption that this procedure has an extremely high safety  
11 rate. Okay? Because what you are basically saying is,  
12 well, it is okay to use this procedure as just one of the  
13 other parts of the armamentarium whereas, if we have a group  
14 that receives ablation and a group that receives hormonal  
15 therapy, and the hormonal therapy gives me as good an  
16 amenorrhea rate when I make a change, or a decrease in  
17 bleeding as the endometrial ablation, and I have a one  
18 percent or whatever percent rate of perforation or  
19 complications--I mean, if we think the inability to do the  
20 procedure is high in the premenopausal, think about the ones  
21 with cervical stenosis, small uterus, higher risk patient to  
22 whatever anesthesia they are going to be given. You know, I  
23 think if we don't compare it to something like hormonal  
24 manipulation and say, oh yes, the outcome is a lot better  
25 then why in the world are we going to put these people at

1 risk, older people at risk for the anesthesia, the  
2 possibility of a failed procedure or whatever complications  
3 come from the procedure, when all we have to do is change  
4 their hormones and we would have done the same thing? So, I  
5 am real leery of using the patient as her own control. I  
6 think we have to have another control, and this procedure  
7 has to be better than just changing her hormones and,  
8 therefore, it is worth taking the risk of the anesthesia and  
9 the possible failed procedure and the possible complication  
10 rate.

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

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

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

24 MS. YOUNG: Let's be realistic about this. Let's  
25 say the studies are done; the device is used in

1 postmenopausal women. The device has been approved for  
2 premenopausal women. The word is going to get out. I can  
3 tell you, I think in the real world you are going to have a  
4 real problem getting the control group, the sort of control  
5 group that you want that isn't going to have this by the  
6 time we are starting to study this because I think that  
7 women are going to know that this is a device that has been  
8 found to be efficacy and safe with premenopausal women.  
9 Great. If it works for them, why can't I have it? No, I  
10 don't want to be randomized out of this study so that, you  
11 know, some women get this and I don't get it because, you  
12 know, I want my bleeding to stop and this has been shown to  
13 work with premenopausal women, well, I want it too.

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

18 I am just concerned about being a little cavalier  
19 in terms of the use of this device in these women where we  
20 have identified a significant set of concerns that are over  
21 and above the premenopausal woman, essentially basically  
22 saying, well, we are just going to use it and then we are  
23 going to figure out what our perforation rate is and what  
24 our complication rate is without really being able to say,  
25 hey, you know, we could have stopped your bleeding just as

1 well by having done this with hormones and not put you  
2 through these risks unnecessarily. That is my concern and  
3 why I definitely would use a control group that would be  
4 some medical manipulation and arrive at the data that way.  
5 You know, if you could do it where you could do then a  
6 crossover, say, after three months or X number of months of  
7 medical manipulation and you still were having problems,  
8 then you would drop into the other arm of the study and go  
9 from there. Somewhat of a crossover; you wouldn't crossover  
10 to the other group.

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

14 DR. BLANCO: Okay.

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

17 DR. BLANCO: But we didn't recommend that. You  
18 did make the statement when we came back to the meeting that  
19 this shouldn't be used sort of very promptly after hormonal  
20 therapy but we really didn't make that statement that you  
21 just made, that you really want medical manipulation prior  
22 to their being able to enroll, and failure of medical  
23 manipulation prior to their being enrolled. So, we are  
24 changing a little bit our answer to number 1(c) there from  
25 what we said before.

1 DR. CHATMAN: I thought it was one of our  
2 requirements for patients to undergo ablation.

3 DR. BLANCO: Maybe I misunderstood that.

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

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

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

24 DR. BLANCO: I can't answer that question. I  
25 don't know if anybody can. Dr. Chatman?

1 DR. CHATMAN: That was my question. I mean, you  
2 know, do we have data on the postmenopausal women with the  
3 hysteroscopic resection? We don't have enough.

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

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

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

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

19 DR. SHIRK: The resection?

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

23 DR. SHIRK: I understand. So they are open-ended  
24 enough to say that it is FDA approved for that procedure if  
25 the physician wishes to use it that way.

1 MS. DOMECUS: But is it the gold standard? Even  
2 if the FDA approval wouldn't limit its use in  
3 postmenopausal, is it the gold standard enough to constitute  
4 a control group?

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

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

8 DR. BLANCO: You mean for the Rollerball?

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

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

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

16 MR. POLLARD: Actually, it is not pre-amendments.  
17 The hysteroscopic resection came into use in the early mid-  
18 80s, but the data that it was based on was premenopausal  
19 women. I don't know precisely the labeling restrictions. I  
20 actually think it is silent with respect to the  
21 postmenopausal situation. Whether or not people consider it  
22 to be an alternative or a gold standard, I actually think it  
23 is probably--well, just to be to the point, the labeling is  
24 silent as far as I know.

25 DR. BLANCO: Well, I think the panel has given the

1 FDA a flavor for the variety and controversy within question  
2 three, and I think we probably have given them all the  
3 controversy and variety--go ahead, and we will move on after  
4 some comments there.

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

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

22 DR. BLANCO: Yes, I think that is very important.  
23 Also there are issues of what does an ablation do in terms  
24 of ability to sample the endometrium if there is later the  
25 development of endometrial hyperplasia or carcinoma? Does

1 it alter the prevalence of the possibility of that  
2 development? I think there are a lot of issues. So, I  
3 think the recommendation there would be that post-market  
4 analyses need to be done to make sure what the follow-up is,  
5 what happens to these women who are ablated and to their  
6 uteri as years pass from their ablation.

7 Any other comments on number three?

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

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

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

1 creating the ablation.

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

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

17 I think also that the mode of creating the  
18 ablation is going to be more critical here. Whether one  
19 uses heat and whether one applies the heat by means of hot  
20 water, electrical discharge, RF heating, or whether one uses  
21 other approaches such as the optimal approach which may, in  
22 fact, be heat, the so-called 360 degree laser, I think all  
23 of these factors are important, plus the distribution of the  
24 source. Perhaps, as we discussed yesterday, multiple  
25 electrodes are a good way to get uniform distribution of

1 heat in the premenopausal uterus. But do the variations  
2 that come from areas over an electrode as opposed to areas  
3 between an electrode, are these sufficiently great in the  
4 thinner myometrium that, in fact, this is cause for concern?  
5 I think all of these kinds of studies would be done in vitro  
6 before one actually goes to a clinical study.

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

22 But I think also in the clinical study you may  
23 want to look at myometrial thickness and have some  
24 parameters of myometrial thickness inclusion or exclusion  
25 criteria, depending on what information is found in the

1 preclinical studies about myometrial thickness and the  
2 effect of the particular device on heat dissipation and so  
3 forth.

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

17 DR. KATZ: I have several comments, sort of  
18 deriving from what Dr. Neumann said. I think we can agree  
19 that this is an area of medicine where there really isn't  
20 the scientific understanding of the system that we would  
21 like to have to design instruments that intervene in it,  
22 especially when we talk about the menopausal uterus but, in  
23 fact, generally speaking even the premenopausal reproductive  
24 tract. There is lots of knowledge of some of the issues  
25 that Dr. Neumann mentioned about the structure of the uterus

1 and how it impacts the effects of any particular ablation  
2 instrument. We just don't have that knowledge.

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

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

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

1 think that is really a critical type of study design that  
2 one would have to do.

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

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

14 DR. BLANCO: Any other comments?

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

1 penetration?

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

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

20           I mean, looking at this sort of realistically, the  
21 majority of them are discarded. I just wonder if there are  
22 studies, physiological studies that have been done, taking a  
23 bunch of these uteri and measuring--using physiologic,  
24 chemical, all sorts of different parameters to measure what  
25 is left now in the old uteri in comparison with the new

1 uteri that have been taken out of premenopausal women? I  
2 don't know if you understand what I am sort of trying to get  
3 at but have we got this information?

4 DR. SHIRK: The answer is who cared?

5 MS. YOUNG: Who did care?

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

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

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

15 DR. NEUMANN: I am not aware of any.

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

21 DR. KATZ: Well, let's work with that a moment.  
22 The same questions apply to the premenopausal uterus. We  
23 are talking about safety issues here. As much by empiricism  
24 as anything else, we believe the data suggests that these  
25 instruments are relatively safe in the premenopausal uterus

1 but that wasn't the result of any fundamental mechanistic  
2 understanding of the properties of these instruments and the  
3 mode of insertion. It was just sort of work done  
4 empirically.

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

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

16 DR. KATZ: Yes.

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

24 DR. BLANCO: I think that brings up the issue of  
25 myometrial thickness, probably the sounding depth of the

1 uterus. All that data needs to be obtained because that  
2 will give you some idea of how to stratify the data that you  
3 get in terms of what you are saying about the smaller uterus  
4 as the woman ages, which is probably more important than the  
5 age per safety and efficacy.

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

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

21 DR. KATZ: I second that, and I wasn't trying to  
22 imply that an awful lot of mechanistic and fundamental  
23 science is the responsibility of a manufacturer. Again, my  
24 feeling is that as long as you can do studies in women  
25 undergoing elective hysterectomy who volunteer to have

1 procedures done prior to hysterectomy, you can learn an  
2 awful lot of meaningful information. But, certainly, FDA  
3 would benefit if there were some stimulation of the science  
4 side of this from other agencies.

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

12 DR. SHIRK: One of the questions that wasn't asked  
13 by the FDA and that I might ask myself, and I don't know how  
14 you feel about the panel answering the question, but it is  
15 long-term follow-up on these patients. That is a safety  
16 issue to me. One of the major safety issues to me is  
17 basically the occurrence of endometrial carcinoma and also  
18 its detection, and whether the panel would want to make some  
19 recommendations as to the post-study follow-up on these  
20 patients, and the length of that obviously. You know,  
21 beyond three years becomes an onerous thing for them in the  
22 premenopausal studies but, yet, three years is not going to  
23 tell us anything about this issue in a postmenopausal study.  
24 So, do we want to make some recommendations on follow-up on  
25 these studies?

1 DR. BLANCO: I think that is excellent. I think  
2 the panel already did that. I think we have said it is very  
3 important to find out what is going on with these patients  
4 in terms of follow-up and development of endometrial  
5 hyperplasia, endometrial cancer and its ability to be  
6 detected. I guess the only issue would be the one you  
7 brought up. Are you going to require more than three years,  
8 and should these patients be followed up longer than three  
9 years? I think there will be a high fall-out rate in terms  
10 of follow-up, but I think in this particular issue with  
11 endometrial hyperplasia and cancer it may be something that  
12 needs to be at least attempted. Any other comments from the  
13 panel?

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

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

22 DR. ROY: Well, I was addressing more the issue of  
23 design first. My second comment is the follow-up of  
24 patients. Three years is inadequate for the purposes of  
25 seeing whether endometrial cancer develops. So, you try to

1 do it as long as you can. I mean, I think that is the only  
2 thing I think we can offer from the point of view of the  
3 panel, that you really need probably 10, 20 years follow-up  
4 for some of these answers to be accrued. Obviously, that is  
5 not going to happen in a rigorous fashion but at least we  
6 should try to develop a tool to at least recommend that  
7 efforts be made to do that.

8 DR. BLANCO: Any other comments from the panel?

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

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

17 MS. DOMECUS: Right.

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

20 MS. DOMECUS: Right.

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



1 suddenly start bleeding. No bleeding for a long period of  
2 time, and I think that it the group where you are going to  
3 see your major pathology come out of.

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

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

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

1 progesterone agent.

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

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

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

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

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

24           The first issue I hope that the committee will  
25 consider when they do their guidance document--Dr. Blanco

1 brought up the point before that we need to use drug therapy  
2 as probably the alternative. The idea of using Rollerball  
3 ablation as an alternative in this group of patients, to me,  
4 seems to be somewhat contradictory in that there is some  
5 degree of risk in endometrial ablation, particularly in a  
6 group that might be cardiac compromised, etc., and the  
7 fluids that we need to use with typical endometrial  
8 ablation. So, I would really strongly urge the committee to  
9 consider not using Rollerball as the other arm for this  
10 study .

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

25 And, then that we consider the fact that in terms

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

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

24 Finally, in terms of the extirpated uteri and pre-  
25 hysterectomy uteri, the pre-hysterectomy uteri--and I am

1 sure the FDA will confirm for all the industry companies who  
2 have worked in this area that they are extremely difficult  
3 to obtain, to do pre-hysterectomy cases. You are asking  
4 patients, and especially now an older woman who is  
5 undergoing a hysterectomy, to have to have temperature  
6 monitors, cirrrosal monitors put on their uterus and delay  
7 their surgical case. So, doing actual in vivo cases pre-  
8 hysterectomy is extremely burdensome and very difficulty  
9 and, frankly, if any of our families were undergoing  
10 hysterectomy, since they are not going to get any benefit  
11 from that, one would have to ask what is the value to the  
12 patient in participating in a pre-hysterectomy study. So,  
13 it is just something to consider in terms of pre-  
14 hysterectomy uteri.

15           Then finally, in terms of the extirpated uteri,  
16 the one risk that I see, and perhaps my industry colleagues  
17 will throw things at me, but the risk that I see in case of  
18 the extirpated cases is that there is some degree of risk.  
19 When we ablate and extirpated uterus there is some degree of  
20 risk that we have now damaged the pathologist's ability to  
21 read that uterus for the potential of future cancer. So,  
22 perhaps in your guidance document you can talk about the  
23 need to hysteroscope that uterus in the lab and do adequate  
24 sampling to be sure that there wasn't a missed occult cancer  
25 before it gets treated in the laboratory.

1           Finally, in terms of long-term follow-up, I think  
2 that Dr. Yin's suggestion is a marvelous one and that  
3 perhaps organizations like the American College of OB-GYN  
4 and the AGL could get involved, as well as the NIH because  
5 the products won't get out there to help the patients that  
6 we want to help if we need to do a 20-year follow-up, and  
7 the difference, frankly, between three and five years of  
8 follow-up, as all of you are aware--by following these  
9 patients for five years we are not going to pick up any more  
10 endometrial cancers. It is a 20-year disease and so I think  
11 leaving it at the three years seems to make reasonable sense  
12 to me. Thank you for allowing me to comment.

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

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

21           Certainly in the latter part of this morning a  
22 number of questions were raised that don't have answers, and  
23 it is appropriate, I guess, for me to mention that the  
24 National Institute on Child Health is actually beginning to  
25 look at the issue of endometrial ablation technologies. In

1 fact, my branch, which is the Contraception and Reproductive  
2 Health Branch, is sponsoring a small working group tomorrow  
3 to discuss what the research needs are in the area to  
4 determine if it fits within the NIH and specifically the  
5 NICHD agenda. That is an open meeting. It has not been  
6 widely publicized because it will be a very preliminary  
7 examination and development of a document which defines  
8 areas that our invited experts feel are the most critical  
9 research gaps. This is not a meeting that will relate to  
10 industry, regulation or approval. It is, in fact, a  
11 research-directed meeting and, as I indicated, very  
12 preliminary.

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

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

23 MS. YOUNG: May I make a comment?

24 DR. BLANCO: Please.

25 MS. YOUNG: I would ask a question of the person

1 who was just here, please. I think it is very fortuitous  
2 that you were here this morning and that you are having this  
3 meeting tomorrow. Are you planning to convey some of the  
4 points that were raised this morning in the discussion, and  
5 take those back to the meeting tomorrow?

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

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

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

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

25 First of all, I would like to commend the panel on

1 their very artful deliberations of this very difficult  
2 topic. It is something that we have put a lot of thought  
3 into also. I believe that Dr. Katz really alluded to the  
4 difficulty of the study design when he stated that there was  
5 a large abundance of postmenopausal uteri available for in  
6 vitro inspection. In fact, patients that are motivated  
7 enough to continue hormone therapy and that continue  
8 bleeding will generally have a hysterectomy as the solution  
9 to their problem.

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

20 However, I believe that Dr. Blanco alluded to a  
21 study design which I think would be appropriate, and that is  
22 a crossover study. Dr. Roy mentioned that these patients,  
23 for inclusion, should have failed modifications of their  
24 hormone regimen. If we accept that as a study group, that  
25 study group could be randomized to either ablation or some

1 further change in hormonal therapy. After a prescribed  
2 period of time, the failures in each group--and as Dr. Shirk  
3 also alluded to, there won't be 100 percent amenorrhea in  
4 the ablation group. You could cross those patients over  
5 into change in hormonal therapy for patients that failed  
6 ablation, or ablation for the patients that failed hormonal  
7 manipulative therapy. I think that that might be a way to  
8 get our hands around this very difficult problem. Thank  
9 you.

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

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

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

25 MS. DOMECUS: Actually, I wanted to make a comment

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

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

23           DR. BLANCO: Any further comments? If not, I want  
24 to thank the panel for another very interesting half day, a  
25 very interesting discussion. I would like to thank everyone

1 at the FDA, as well as everyone from the public and industry  
2 for all their comments.

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

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

## 1 AFTERNOON PROCEEDINGS

2 **Introduction**

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

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

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

23 I am the chairman of the panel. I am Jorge  
24 Blanco. I am a Professor and Associate Chairman of the  
25 Department of OB-GYN at the University of Florida,

1 Pensacola, and the Medical Director at Sacred Heart Women's  
2 Clinic in Pensacola, Florida.

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

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

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

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

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

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

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

25 DR. SHARTS-HOPKO: I am Nancy Sharts-Hopko,

1 Professor in the College of Nursing at Villanova University,  
2 Villanova, Pennsylvania.

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

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

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

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

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

24 DR. BLANCO: Thank you. At this point I would  
25 like to introduce Mr. Colin Pollard. Mr. Pollard is the

1 Chief of Obstetrics and Gynecology Devices Branch, Center  
2 for Devices and Radiological Health, in Rockville, Maryland.  
3 He will be doing an introduction and general update, and  
4 giving us some sense of where the panel discussion is to  
5 begin.

#### 6 Introduction and General Updates

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

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

20 That committee made a couple of recommendations.  
21 Actually, it made six or seven recommendations, one of which  
22 was to issue a public health advisory, of which you have a  
23 copy in your folder. That was issued May 21st. Another  
24 recommendation from that ad hoc committee was to provide  
25 specific labeling guidance to manufacturers of fetal vacuum



1 for the agenda. Also, if you have not already done so, if  
2 you would please give a hard copy of your overheads, slides  
3 and written statements to the FDA, Mr. Yung Pak, who will be  
4 happy to receive those and they can become part of the  
5 formal proceedings.

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

10 [No response]

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

15 DR. VACCA: Yes, I am.

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

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

24 [Slide]

25 As I mentioned, I made a life-long study of vacuum

1 extraction, dating back for more than 30 years, and from the  
2 very beginning of the modern era of vacuum extraction, which  
3 dates back to a little over 40 years, there have been  
4 reports of adverse outcomes associated with this device,  
5 this one dating back to 1962.

6 [Slide]

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

11 [Slide]

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

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

25 [Slide]

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

13           [Slide]

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

22           [Slide]

23           The other area that I would like to touch on is in  
24 the selection of patients who are suitable for this  
25 procedure. I would like to describe the process that I use

1 to select the women who are suitable and those who are not.  
2 I look for these key obstetrics factors, namely, arrest of  
3 descent, station of the head, the condition of the fetus,  
4 the degree of molding, the position of the baby's head in  
5 the pelvis. For station and position I use the ACOG  
6 recommendations.

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

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

21           [Slide]

22           Finally, it is our challenge to make this  
23 procedure as safe as possible for mothers and their infants.  
24 I have mentioned but two ways in which we might attempt  
25 this, but the way toward a better outcome has been well

1 documented. The bottom line is training and more training.

2 Can I ask you, how many of you would allow someone  
3 to perform a forceps delivery without appropriate training?  
4 Why shouldn't we expect the same for vacuum extraction?

5 Thank you.

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

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

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

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

16 DR. BLANCO: You have to use the mike.

17 [Slide]

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

20 [Slide]

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

1 shape. You saw that also on Dr. Vacca's slide.

2 [Slide]

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

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

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

25 [Slide]

1           This slide is the current use of vacuum extraction  
2 devices. It is estimated in about 10 percent of deliveries.  
3 In brief, indications are fetal distress and prolonged  
4 second stage and I will talk a little bit more about that in  
5 a moment. Preferred assisted device with transverse arrest.  
6 That was documented in a research study by Dr. James Bofill  
7 in December of 1996. It is estimated to be used in about 5-  
8 7 percent of cesarean deliveries.

9           [Slide]

10           On this slide you see the use of vacuum assisted  
11 devices in cesarean deliveries, if we can talk about that  
12 for just a moment. Since you already have the slides ahead  
13 of you, I will go on. Prism has no reported incidence of to  
14 date of any injury that has occurred when a vacuum extractor  
15 has been used during a cesarean section. The indications  
16 have been stated as a high floating head, which can clearly  
17 be stated as an elective repeat cesarean. The advantages  
18 here are that you do not have to use extreme fundal pressure  
19 to push the baby down and in a position that can easily be  
20 extracted. You do not have to use your hands in trying to  
21 grab the head and to extract the baby out, which can be  
22 slippery and difficult. So, the advantages are as stated.  
23 It decreases the uterine manipulation and the risk of  
24 extensions into the lower uterine segment, thus reducing the  
25 risk of hemorrhage for the mom.

1 [Slide]

2 We are all driving for a healthy outcome, and I  
3 have just a few bullet points as to how we hope to  
4 accomplish that: Use appropriate indications. We have  
5 stated them, and on the back of this brochure you will note  
6 that we have recommended guidelines, as well as indications.  
7 You also should have been copied on our operational  
8 guidelines that are included in our sterile packaging.  
9 These are the indications that we use today: fetal status,  
10 failure to deliver spontaneously, maternal need to avoid  
11 voluntary expulsive efforts, any kind of cardiac or stroke  
12 risk for mom, and inadequate expulsive efforts.

13 [Slide]

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

21 I did review the template and noted that you all  
22 have clearly stated that. Also, I noted that we should  
23 allow the manufacturers to provide product specific  
24 operational guidelines, as you will note. Because of the  
25 cup shapes and designs, it is very important that we are

1 allowed to tell them how to get the best results and to  
2 ensure safety. You all should have the operational  
3 guidelines, if you need any reference on the bell versus the  
4 mushroom shape.

5 [Slide]

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

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

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

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

22 MR. JOHNSON: My name is Sam Johnson. I am the  
23 marketing manager for the obstetrical products line for Utah  
24 Medical Products, and we are a supplier of the cups to the  
25 industry.

1           An outline of my points of discussion has been  
2 distributed by Dr. Harvey, and there are two basic areas.  
3 One is a history of CMI and the second would be issues  
4 related to safe utilization of the vacuum systems.

5           Utah Medical acquired CMI in July of 1997. So we  
6 have owned them for approximately a year and three months  
7 now. CMI has focused on vacuum extraction since 1982, when  
8 they originally began as a distributor for Mityvac, then  
9 beginning in 1988 as an independent manufacturer. Since  
10 1988, CMI developed vacuum extraction products on which it  
11 holds five patents, the most significant of which is related  
12 to soft silicone bell-shaped cups.

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

20           In light of that, we feel that there are two major  
21 areas associated with safe utilization. One is physician  
22 technique. To assist physicians in use of a proper  
23 technique, Utah Medical has provided several things for  
24 educational purposes. Again, these should be included in  
25 the handouts.

1           The first is an expanded instructions for use,  
2 which constitutes four pages of instructions and one is  
3 included in every box of product.

4           Secondly, a condensed instructions for use on an  
5 8.5 by 5.5 card, printed front and back, in each container  
6 or each pouch of vacuum cups.

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

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

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

20           Also, in light of possible failures to abort the  
21 actual vacuum delivery attempt and an unwillingness to give  
22 up on the procedure when things aren't progressing as they  
23 should, we feel, in the near term, that soft bell-shaped  
24 cups will release from the fetal scalp sooner than a  
25 mushroom-shaped cup when an excessive or misdirected or

1 otherwise inappropriate force is applied and, therefore, the  
2 cup will provide better protection to the infant from  
3 serious injury.

4 Are there any questions?

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

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

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

21 One is that the number of reported deaths and  
22 injuries associated with vacuum deliveries is relatively  
23 small considering the total number of deliveries in the  
24 United States each year. Although there may be an under-  
25 reporting of the morbidity associated with these devices,

1 the exact incidence of this morbidity is difficult, if not  
2 impossible, to actually calculate considering we really  
3 don't know what the denominator is. We have a lot of  
4 estimates as to how often these devices are used, but we  
5 really don't have any hard numbers, and the frequency of  
6 vacuum delivery, from the literature, ranges from 0.3  
7 percent to as high as 6.2 percent.

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

23           We would like to make the following  
24 recommendations regarding future labeling, and most of these  
25 have been included in the preliminary labeling that I have

1 seen:

2           The operator or teacher must be appropriately  
3 trained, experienced and skilled in the use of these  
4 devices.

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

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

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

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

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

23           The risk of routine vacuum application at the time  
24 of cesarean delivery is unknown and should not be done  
25 routinely.



1 today is, number one, to explain what prompted the FDA to  
2 issue this public health advisory; number two, to explain  
3 how the process within the FDA worked; how the ad hoc  
4 committee came to its recommendations and what the  
5 recommendations were, and what parts of those  
6 recommendations we have completed so far.

7 [Slide]

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

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

23 If you follow this slide, we can see that in year  
24 1993 we received two reports. Then, all of a sudden, in  
25 year 1994 we received six reports of the adverse events

1 associated with the vacuum assisted delivery devices. In  
2 1995 we received three; in 1996, again six reports, as well  
3 as in year 1997.

4 [Slide]

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

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

18 [Slide]

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

24 [Slide]

25 Based on information that we could find in those

1 reports, we realized that we cannot point really toward one  
2 particular device, nor at one particular manufacturer, nor  
3 at one specific type of cups. Not to mention that in our  
4 database we did not have really have access to the most  
5 critical information about the clinical situation that  
6 surrounded the application of this device.

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

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

20           Finally, we also realized that we cannot act  
21 alone, and we needed to consult with professional  
22 organizations, including the American College of  
23 Obstetricians and Gynecologists, the American Academy of  
24 Family Physicians, American College of Nurse Midwives,  
25 American Academy of Pediatrics.

1 [Slide]

2 As I said, we wanted to make sure that we  
3 understand what the entire picture is. So, this is the most  
4 recent estimate nationally that we could obtain from the  
5 National Center for Health Statistics that was published in  
6 1997, and which reflected the increase in the use of vacuum  
7 assisted delivery devices from year 1989. It was 3.5 in  
8 1989 and, as you can see, in year 1995 it was 5.9. These  
9 percentages actually reflect the percentages of the entire  
10 number of deliveries in the United States. In year 1989 we  
11 had 3.5 percent of vacuum use out of all numbers of  
12 deliveries versus 5.9 percent in year 1995.

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

18 [Slide]

19 As a group, we have concluded after reviewing the  
20 literature, reviewing the reports, discussing with  
21 manufacturers, users and professional organizations that the  
22 possible reasons for an increased number of adverse event  
23 reports associated with vacuum assisted delivery devices  
24 could be the following: Increase in use of the device, and  
25 I have just pointed out the national estimates of that.

1           Also, we realized that some changes in the  
2 reporting system might have contributed to the increased  
3 number of reports. Predominantly, I have in mind the use of  
4 user facility reporting data which became effective in 1992.

5           Also, we cannot neglect the potential under-  
6 reporting in previous years. Also, finally, the real  
7 increase in the incidence rate of adverse events.

8           [Slide]

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

14           We also need to publish an article in the FDA's  
15 column in JAMA, and we did that in the July issue of JAMA  
16 where we basically summarized the public health advisory.

17           Also, we decided that we need to look into the  
18 promotional claims regarding the ease and safety of vacuum  
19 assisted delivery devices. We thought it is important to  
20 invite manufacturers to discuss the agency's concerns  
21 regarding the adverse effects of the device, and also to  
22 revise the labeling of the devices to include warnings  
23 regarding specific complications, the thing that we will be  
24 discussing today and, finally, to propose and encourage  
25 academic, user and/or industry research of complications

1 associated with the device.

2 [Slide]

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

10 [Slide]

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

18 [Slide]

19 I am not sure how clear this is going to be, but  
20 you also have copies in your handouts. This slide actually  
21 shows the location of the injury when subaponeurotic  
22 hemorrhage occurred. Basically it is between this dense  
23 membrane and periosteum. What is important to point out  
24 here is that this doesn't contain any boundaries so if the  
25 injury of the emissary vein were part of that region, then

1 the bleeding can spread and the volume of blood is almost  
2 the same as the fetal blood volume. So, that is why we felt  
3 it is important to point out the most dangerous and fatal  
4 complications of the use of the device.

5 [Slide]

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

13 [Slide]

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

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

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

25 Also, educate the neonatal care staff about the

1 complications of this device, and, of course, report all the  
2 adverse events associated with this device to the FDA.

3 Thank you.

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

7 DR. MITCHELL: Good morning.

8 [Slide]

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

14 [Slide]

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

21 The Code mandates that the FDA require adequate  
22 labeling to provide a trained user with the information  
23 needed to use that particular device properly. It is  
24 important also to understand that this information does not  
25 need to be in its entirety for use of the device.

1 [Slide]

2 The labeling template is a guidance for  
3 manufacturers to use when labeling a device. Today, during  
4 my talk you will hear me use the terms guidance and  
5 template. I will be using them interchangeably.

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

12 [Slide]

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

20 [Slide]

21 The indications that the FDA has chosen in the  
22 Branch are listed above. Now, before I say what they are, I  
23 just want to take a minute to explain our rationale. Our  
24 goal was to condense the indications into a few broad  
25 categories. In the next few slides you will see what are

1 considered to be subcategories of these particular  
2 indications. What I hope the purpose of the discussion  
3 today will be is to not only look at these indications that  
4 we have listed, but the subcategory indications, and make  
5 sure that we have the right group of indications and, if  
6 not, revise those.

7 [Slide]

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

13 [Slide]

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

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

23 An indication that was felt to be both maternal  
24 and fetal, failure to deliver spontaneously following and  
25 appropriately managed second stage.

1 [Slide]

2 The indication of non-reassuring fetal heart rate  
3 pattern was felt to be inclusive of the subcategories of  
4 fetal distress as evidence by a significant deceleration  
5 persisting well after the contraction. Fetal compromise was  
6 related to intrauterine growth retardation, IUGR,  
7 oligohydramnios preceding labor. Fetal compromise as related  
8 to cord entanglement, acute fetal distress and presumed  
9 fetal jeopardy.

10 [Slide]

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

17 [Slide]

18 The indication of cord prolapse and abruption did  
19 not have any specific subcategories. They were put up there  
20 as separate indications only because in the literature they  
21 would be mentioned in the context of these may be  
22 appropriate indications to do a vacuum extraction with an  
23 incompletely dilated cervix; or at a level higher than  
24 outlet presentation.

25 [Slide]

1           So, there are other indications that we chose not  
2 to list. However, we would appreciate a discussion of them  
3 as to whether they would be appropriate or not. These other  
4 indications include cesarean section; borderline  
5 cephalopelvic disproportion; incompletely dilated cervix;  
6 mid or high pelvis extraction, recognizing that these don't  
7 go together; elective and unengaged fetal heart.

8           [Slide]

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

20           [Slide]

21           The next section in the labeling guidance is  
22 warnings. These are all the warnings that are listed in the  
23 guidance. What I wanted to bring out for you are the areas  
24 that are underlined. I hope you can see that underlining in  
25 the slide.

1           Specifically, the first point recommends that we  
2 limit the use of the vacuum device to individuals with  
3 experience in the use of vacuum extractors.

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

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

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

16           [Slide]

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

24           [Slide]

25           The fetal adverse events--and attempt was made to

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

7 [Slide]

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

16 [Slide]

17 This is sub-section one of the clinician use  
18 information. What we found in specifically looking at the  
19 literature and the ACOG Technical Bulletin of 1994 is that  
20 not only were there indications and contraindications, but  
21 there were what has been termed prerequisites to vacuum  
22 assisted delivery, in other words, circumstances surrounding  
23 the hospital, the patient or the operator that are necessary  
24 in order to conduct a safe and effective trial of fetal  
25 vacuum extraction.

1 I will read these for you. Again, this is a draft  
2 list and we welcome and encourage discussion. Knowledge of  
3 the mechanism of labor by the operator; knowledge of the  
4 actual course of labor of the patient who requires vacuum  
5 assisted delivery; know as precisely as possible the  
6 station, position and attitude of the fetal head; engaged  
7 fetal head; no demonstrable clinical cephalopelvic  
8 disproportion.

9 [Slide]

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

14 [Slide]

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

21 However, we wanted to give an idea of how this  
22 labeling should be done, and that is the function of a  
23 guidance. The preparation section reinforces the idea that  
24 the exact knowledge of the fetal position is critical.  
25 Conduct a vaginal examination to confirm the degree of

1 dilation and effacement of the cervix. The condition of the  
2 membranes, the presentation and position with reference to  
3 the size and shape of the birth canal.

4 [Slide]

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

10 [Slide]

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

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

25 [Slide]



1 until you get to the microphone.

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

7 DR. ROY: Thank you.

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

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

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

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

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

1 the discussion.

2 DR. MITCHELL: Question one, indications for use:

3 (a) Please comment individually on each listed indication:

4 Prolonged second stage labor; non-reassuring fetal hart rate  
5 pattern; maternal medical illness that prohibits adequate  
6 second state labor; placental abruption; cord prolapse.

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

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

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

23 I thought what we might do is actually use Dr.  
24 Mitchell's slides because there is more detail in her slides  
25 concerning the actual subset under each of these listed

1 indications, plus, you do have them in your folder but can  
2 we bring in the more detailed ones, please? The one that  
3 has the subset?

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

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

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

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

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

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

22 [Laughter]

23 DR. BLANCO: I am turning it right back to you. I  
24 don't have the answers. I mean, do we want to make it a  
25 time limit or do we want to say in the judgment--you know,

1 essentially, should this instrument be utilized if you have  
2 maternal exhaustion at 30 minutes, or do you want to make  
3 them wait two hours because you are going to define  
4 prolonged second stage as two hours? Dr. Allen, what do you  
5 think?

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

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

17 DR. ALLEN: Right.

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

19 DR. ALLEN: I am going on, and I think the last  
20 two items under maternal--inadequate contraction activity  
21 leading to failure to descent and rotate really lends itself  
22 to a strict definition, or this is what you are looking at  
23 in explaining your prolonged second stage, as well as  
24 uterine inertia. These are all definitions of dysfunctional  
25 second stage, those last two items. So, those are clear-

1 cut.

2 I think the more ambiguous items are the first  
3 three, and I think we need to decide, if we want to decide  
4 if they are indications in and of themselves, and are there  
5 other ways of addressing this rather than putting a vacuum  
6 on. As you said, with excessive analgesia, do you just let  
7 the epidural wear off? Do you decrease it?

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

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

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

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

25 DR. BLANCO: So, essentially, if I read you

1 correctly, your suggestion is not to put a time limit since  
2 some of these wouldn't be improved with a time limit  
3 necessarily, namely, the first, second and the fourth and  
4 fifth. Then, the question is whether for excessive  
5 analgesia that is even a significant one that we ought to  
6 include in there. Does that summarize it? Anyone else have  
7 any opinions? Dr. Mitchell would like to say something.

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

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

1 as a definition of it.

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

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

24 MS. YOUNG: Could I comment? I think we have some  
25 real problems with the terms that are up there as being

1 subgroups. There has always been professional disagreement  
2 about what dystocia is and what it is not. It has been  
3 called sort of an umbrella term. I mean, NIH years ago  
4 tried to grapple with what dystocia was. You know, to see  
5 it up there under fetal indications as opposed to maternal  
6 indications--certainly, definitions of dystocia could be  
7 called maternal indications. So, I think it is going to be  
8 extremely difficult to deal with that unless this group and  
9 the FDA comes to a decision about what a definition of  
10 dystocia is. As I say, professional groups, NIH, everybody  
11 else, individual practitioners, can't decide what dystocia  
12 is and what it is not.

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

17 DR. BLANCO: I think, you know, that might be a  
18 suggested terminology. I guess my issue, as still a  
19 practicing obstetrician at times, I know that vacuum has  
20 been used, and probably appropriately, for some of the  
21 subsets there, and I guess I would not have considered them  
22 to have been necessarily because I had a prolonged second  
23 stage or maybe a failure. I guess I would disagree with  
24 Subir. You may have someone who is exhausted and has  
25 progressed in the second stage, and you may want to

1 terminate that delivery if it is a low and inappropriate  
2 presentation. You know, if we say failure of the second  
3 stage of labor, that may not fit in there if we are trying  
4 to be purists about it. Dr. Chatman?

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

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

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

22 I am just wondering if you want to pull out as a  
23 separate indication maternal exhaustion, and pull out as a  
24 separate indication lack of cooperation, and not put them  
25 under prolonged second stage.

1 DR. BLANCO: Well, I will tell you what I think we  
2 need to do. I think we need to come up with what we think  
3 the indications are and they can divvy it up and put it in  
4 an outline or whatever form they want, and what we ought to  
5 say is are these things for which a vacuum procedure  
6 reasonably might be done and work as an indication. I think  
7 from what everyone has said, the one thing they have agreed  
8 is about the only one that had any controversy was the  
9 excessive analgesia; that all the others no one would have a  
10 problem with a vacuum extraction as an indication. Is that  
11 correct? Go ahead, Dr. Chatman.

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

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

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

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

25 DR. BLANCO: Okay. So, you would go for leaving

1 it in?

2 DR. CHATMAN: All things being equal, sure.

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

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

10 DR. BLANCO: Right.

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

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

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

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

20 [Laughter]

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

1 DR. BLANCO: Huh, that helps!

2 [Laughter]

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

21 MS. YOUNG: Yes.

22 DR. ALLEN: Do you want that under fetal?

23 DR. BLANCO: I wouldn't put it under fetal. I  
24 would put it under maternal; maternal-fetal. Again,  
25 dystocia due to lack of flexion--I would probably take the

1 word dystocia out and say arrested descent due to lack of  
2 flexion. I think that is really what we mean and that  
3 probably, again, doesn't belong under fetal but probably  
4 under maternal or maternal-fetal.

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

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

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

25 DR. ROY: In and of itself, I don't think it is a

1 reason. We are only indicating it in its presence and with  
2 inappropriate or insufficient labor. Then it would be an  
3 indication but not in an of itself.

4 DR. BLANCO: What do you all think?

5 DR. CHATMAN: I would agree with that. There are  
6 other strategies for managing occiput posterior too.  
7 Perhaps those should be taken into consideration as well,  
8 not only lack of descent but failure of other strategies to  
9 convert an occiput posterior to an anterior.

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

14 DR. ALLEN: Yes.

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

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

24 DR. BLANCO: I suspect it has probably gotten out  
25 of prior indications that someone put. No, I don't think we

1 need to make her come up every time to tell us that.

2 Yes, I think it is fairly general statement. It  
3 is probably appropriate because it gives physicians an  
4 ability to make a medical judgment, which is what we want.  
5 We don't want to interfere with medical judgment; we want to  
6 regulate the device. The reality is you want to do  
7 something if you have a failure to deliver and you have  
8 appropriately managed second stage. So, maybe it should go  
9 at the top as a major indication. That looks like a  
10 consensus. So, we can move on. Anything else? Anything  
11 that we want to add in terms of prolonged second stage?  
12 Anything that might fit under here? No takers?

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

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

18 DR. BLANCO: Why not?

19 DR. ROY: Well, I think obstetricians will make  
20 judgments according to however the fetal distress comes  
21 about. The distinction will be whether the labor has  
22 progressed sufficiently to facilitate prompt delivery with  
23 an operative outlet delivery versus a cesarean section. So,  
24 a non-reassuring fetal heart rate pattern that can be  
25 addressed quickly and promptly with outlet delivery,

1 whatever the indications are.

2 DR. CHATMAN: I was just wondering, I think the  
3 non-reassuring fetal heart rate pattern is there in order to  
4 avoid fetal distress, and we have fetal distress in here  
5 twice and I think it might be a good idea to use other  
6 terminology.

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

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

17 DR. BLANCO: Right.

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

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

25 DR. CHATMAN: No, what I was saying was that we

1 haven't determined that the baby is compromised. We know  
2 the fetal heart rate is abnormal but we don't know that the  
3 baby is compromised in many situations.

4 DR. BLANCO: Right.

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

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

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

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

1 fetal heart rate tracing good enough as the big heading?

2 DR. CHATMAN: For me, the latter.

3 DR. BLANCO: Fetal compromise--

4 DR. CHATMAN: No--

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

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

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

21 DR. BLANCO: No; that is not out of vogue. I have  
22 the same problem but I don't know that I would fix it,  
23 necessarily, but using lates because I think, again, you are  
24 going into the judgment of the physician interpreting the  
25 fetal heart-rate strip and making a decision on is this baby

1 in trouble that needs to be delivered now or have I got more  
2 time.

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

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

16 Does that make any sense?

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

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

24 DR. ALLEN: Can we take out the specific  
25 etiologies like IUGR and oligohydramnios and cord

1 compression? I don't think--

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

6 DR. ROY: No.

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

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

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

22 DR. BLANCO: Yes; and 2 and 3 seem, to me, to be  
23 the same thing. They seem to be just a restatement.  
24 Anything else on this one? It seems fairly straightforward.

25 All right. We are progressing well. The next

1 one; placental abruption and cord prolapse. No pun intended  
2 on "progressing well." Placental abruption and cord  
3 prolapse. What do you all think about those?

4 DR. CHATMAN: They are bad things.

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

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

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

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

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

23 If you have got a stable placental abruption, a  
24 mother who is progressing in labor, do you really need to  
25 intervene? Is that an indication to intervene?

1 DR. CHATMAN: It could be acute and progressing.  
2 If you can make a diagnosis of abruption and the baby is  
3 still okay and she is completely dilated and a plus 2, why  
4 wait?

5 DR. BLANCO: So you would leave it in?

6 DR. CHATMAN: I think so.

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

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

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

23 Give your opinion, Dr. Allen.

24 DR. ALLEN: It just seems to me when we have had a  
25 cord prolapse, we have pushed the head up and delivered

1 abdominally. Since I have never been in this situation  
2 where I have had a cord prolapse with full dilatation at  
3 plus-2 or plus-3 station--usually, as you say, the cord  
4 prolapse is before the cervix is fully dilated.

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

8 DR. CHATMAN: An occult cord prolapse.

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

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

16 DR. BLANCO: All right.

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

19 DR. BLANCO: Both of these?

20 DR. ALLEN: Yes.

21 DR. BLANCO: Anybody feel strongly--

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

24 DR. BLANCO: And they are likely to fit under one  
25 of the other criteria that we have already agreed to. So we

1 are not happy with abruption or cord prolapses as  
2 indications.

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

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

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

25           I am very concerned about incompletely dilated

1 cervix, high pelvic extraction and elective use and  
2 unengaged head, which is--that is high-high. That is really  
3 high. I think those are problematic for me to include them  
4 as indications. I think we ought to treat the instrument  
5 essentially similar to forceps. I would have some problems  
6 with those.

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

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

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

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

22 DR. ROY: Dr. Gilstrap, I think, mentioned that  
23 the ACOG position was directly in opposition to that. Did I  
24 phrase the ACOG position on that, the use of vacuum at the  
25 time of C-section?

1 DR. HARVEY: Dr. Gilstrap, please come up to the  
2 mike. Thanks.

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

6 DR. BLANCO: Thank you.

7 Let's take a five-minute break.

8 [Break.]

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

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

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

25 DR. GILSTRAP: Just really quickly. I think on

1 the indications, a good easy way to handle this would be to  
2 put them under maternal indications and fetal indications,  
3 just two broad categories. Most of those would fit nicely.

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

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

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

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

25 MS. YOUNG: Can I add to that borderline CPD?

1 What is borderline CPD? If anyone can give me a definition  
2 of that--

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

8 How does the rest of the panel feel?

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

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

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

22 Larry, do you know of any data using it?

23 DR. GILSTRAP: No; I am not aware of any data. I  
24 know a lot of clinicians say they use it and I always ask  
25 them how do you get it on correctly at that time unless the

1 head is just presenting just perfectly for you to do that.

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

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

11 DR. ALLEN: Yes.

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

14 MS. YOUNG: I have a problem with that.

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

18 DR. ALLEN: You can think of it the same way you  
19 can think of elective forceps, that you would like for  
20 someone to be well versed and familiar with the instrument  
21 prior to being in an emergent situation. So, perhaps, there  
22 is a teaching role for learning how to place this on the  
23 head at what station and what kind of traction forceps to  
24 use. That is the only time I can see using it electively  
25 is in instructing someone who is progressing nicely with a

1 nice unmolded head where the landmarks are easily palpated  
2 and just going through the motions.

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

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

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

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

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

20 DR. BLANCO: Even though it is not one of the  
21 questions, I think that if the panel would agree, I think  
22 that the suggestion that this instrument, unless proven  
23 otherwise with further data, should be considered  
24 essentially similar to what we do with forceps. This is  
25 probably a very reasonable type of approach.

1           How does the panel feel about that as a  
2 recommendation to the FDA? Okay? So using the nomenclature  
3 that we use for forceps, et cetera, would be useful.

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

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

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

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

25           DR. BLANCO: Would you put in just "prematurity?"

1 DR. GILSTRAP: Yes. I don't have a lot of data  
2 for this, but a lot of people say less than 32 weeks. I  
3 hate putting numbers and things on it.

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

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

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

24 DR. GILSTRAP: Then it probably ought to stay that  
25 way, extreme. I agree.

1 DR. BLANCO: Stay with extreme maturity?

2 DR. GILSTRAP: Right.

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

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

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

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

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

1 after a fetal scalp pH.

2 I have absolutely no idea how to define it.  
3 Again, this is one of the things where we I think we are  
4 trying to make reasonable decisions on theoretical issues  
5 that make sense and that are common sense but where I think  
6 data would be very, very helpful to have and to obtain.

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

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

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

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

24 DR. GILSTRAP: But I think it would be better  
25 under a warning and not as an absolute contraindication

1 because, again, it is very unlikely that a baby is going to  
2 bleed to death from putting--that you are not going to see  
3 hemorrhage from--

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

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

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

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

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

23 DR. CHATMAN: Maybe this ties into what I was  
24 thinking about as another contraindication. I don't know  
25 whether it is pertinent or not, but a known macrosomic

1 infant; are we going to be able to use a vacuum in that  
2 circumstance? Then you get into the definition of what  
3 macrosomic is, 4,000 or 4,500 grams and the size of the  
4 pelvis and stuff like that.

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

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

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

24 I think what we are looking to do is to prevent  
25 these untoward events. I appreciate what you are saying

1 about putting in cautionary notes as opposed to absolute  
2 contraindications but I think this is significant. I think  
3 CPD is a significant contributor to bad events, that it  
4 should stay in.

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

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

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

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

15 DR. CHATMAN: What about macrosomia.

16 DR. BLANCO: Let's talk about macrosomia.

17 DR. CHATMAN: Is that not considered a--

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

22 DR. GILSTRAP: Why don't we put "fetal pelvic  
23 disproportion."

24 MS. YOUNG: Yes; that would be better.

25 DR. BLANCO: That would be a better way and that

1 would include your macrosomia on that. That is an excellent  
2 suggestion. Excellent.

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

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

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

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

22 DR. BLANCO: I think maybe not here but I think  
23 somewhere it is experienced operator or supervisor. I guess  
24 that is in the other one. So maybe what we need to do is  
25 add that to this part, someone without experience in vacuum

1 delivery or without supervision by someone with experience  
2 in vacuum delivery. I think it is very difficult.

3           You have brought up a point that hospitals wrestle  
4 with in terms of staff privileging and privileging for  
5 procedures. I don't think that we can get into that. I  
6 think what we need to regulate is we need to say there  
7 should be a level of experience that residents should be  
8 being taught, that physicians who are going to use this  
9 instrument need to have.

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

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

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

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

24           You are no happier with that?

25           MS. YOUNG: No. I am throwing it out because I

1 see it as being an impossibility, really, to define.  
2 Experience needs to involve, actually, not experience with  
3 the equipment with experience with using the equipment--that  
4 is, doing the procedure. I think that that needs to be  
5 incorporated in the wording.

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

13 Anyone feel differently?

14 DR. GILSTRAP: Pretty straightforward.

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

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

19 3; the draft labeling template also addresses  
20 warnings, precautions, adverse events, patient counseling  
21 information and clinical-use information. Please comment on  
22 each of these sections. If we could please put those  
23 sections up. Who wants to start with some comments?

24 DR. MITCHELL: Dr. Blanco, before we get started,  
25 just to point out, question 4 is asking to deal specifically

1 with the prerequisite section of clinician use, if you want  
2 to separate that out later.

3 DR. BLANCO: Okay.

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

15 DR. ALLEN: Actually, there is a review article by  
16 Plauche which is talking about--I think it was this one. It  
17 was a prospective study that we read where there were about  
18 300 deliveries in both arms, the control and the vacuum. In  
19 the vacuum-assisted arm--and both had pretty good results,  
20 comparable results. The accrued time was 20 minutes. So I  
21 was wondering where the ten minutes came from.

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

24 DR. MITCHELL: There is no particular magic about  
25 ten minutes. Again, we looked at the information that we

1 had available to us which included the things that we have  
2 approved previously in the literature and the number--ten  
3 minutes was mentioned. Twenty minutes has also been said.  
4 This number is up for discussion.

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

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

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

22 Pretty soon, it is going to be very difficult for  
23 you to tell how much time you have had the vacuum up and how  
24 much you have had it long. Again, I hate to make some  
25 arbitrary cutoff if we don't really have some hard data to

1 show that we have got a worse outcome afterwards because I  
2 think, otherwise, we are practicing a little medicine and  
3 maybe practicing a little medical-legal medicine with doing  
4 this.

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

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

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

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

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

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

25           DR. ALLEN: This is actually 1979, in June. They

1 had, in the summary and conclusions, they had some edematous  
2 scalp lesions which were unavoidable, abrasive and  
3 ecchymotic lesions can be reduced by keeping the negative  
4 suction to a maximum of 0.7 kilograms per centimeter  
5 squared, shortening the time of cup application to a maximum  
6 of 20 minutes and avoiding pulloffs of the suction cup.

7 Our experience indicates that a large vacuum-  
8 extractor cup induces fewer superficial scalp lacerations.  
9 So this is an article written in 1979.

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

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

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

22 DR. CHATMAN: Do we have any information to  
23 suggest that ten minutes of accrued time is dangerous,  
24 twenty minutes of accrued time is dangerous, thirty minutes  
25 of accrued time is dangerous? We don't really have the

1 right to make a statement about accrued time. We don't have  
2 any information.

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

7 DR. CHATMAN: I think that is good.

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

11 DR. CHATMAN: Yes; a reasonable time.

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

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

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

23 DR. NEUMANN: I would just like to remind the FDA  
24 of some basis physics, that we can't consider any of these  
25 factors individually because they are all related. The

1 amount of pressure alone is not sufficient because you have  
2 to consider the surface area of which the pressure is  
3 applied to get the net force. The net force is related to  
4 the traction force that is applied.

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

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

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

22           I think the other issue that you made earlier, but  
23 I want to reiterate again, was that, probably if the  
24 determination of some of these numbers such as how high or  
25 how low to lower the pressure are more empiric than some

1 statement to that effect and how it was decided it should be  
2 arrived at so that is well documented.

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

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

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

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

19           Again, we are pulling numbers out of a hat. I  
20 don't think we have got data to show--and I guess the  
21 important thing would be can we obtain data and should we  
22 monitor the number of popoffs to see whether there is a  
23 relationship between--and this is a suggestion--whether  
24 there is a relationship between the cup popping off and the  
25 rate of adverse events.

1 DR. GILSTRAP: The way it is touted by  
2 manufacturer and in the literature is that the reason it is  
3 safe is it pops off if the baby is too big and the pelvis is  
4 too small. So that is the way it is touted.

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

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

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

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

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

22 DR. BLANCO: There wasn't one. I suggested two.  
23 They have three. I have put my rationale. Dr. Chatman has  
24 six. He likes the number 6. Do we want to make a  
25 conclusion, address that?

1 DR. KATZ: It is a matter of relevance but it is a  
2 matter for which there is no unique answer; right?

3 DR. BLANCO: Right.

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

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

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

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

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

24 DR. ALLEN: I don't even know if you need to put a  
25 time frame on that. If, after proper application, the cup

1 pops off, then reassessment of the utility of this  
2 instrument is in order.

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

5 DR. BLANCO: Lots of people.

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

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

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

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

20 DR. GILSTRAP: I would say, "Always pull in  
21 synchronization with contractions or patient's expulsive  
22 efforts or pushing," either/or.

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

25 Post-delivery precautions. Should the neonatal

1 nursery be advised? Yes. We probably don't do it enough.

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

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

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

21 So if we are really saying "never" to those two,  
22 should we not move those up either into the warning or into  
23 the contraindication category. If not, should we, instead,  
24 say not "never," but say, "Do not use rocking movements. Do  
25 not apply torque."

1 I'll tell you, I never was taught to do either one  
2 and never had even considered doing either one.

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

7 DR. CHATMAN: What is a rocking motion?

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

14 What level do we want to put these at?

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

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

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

24 DR. ROY: Not or never makes not difference from  
25 the clinical point of view. That is an absolute statement.

1 DR. ALLEN: We can bring it up to the maternal  
2 soft tissue; do not involve any maternal soft tissue. I  
3 think maternal soft tissue in the cup should be an absolute  
4 contraindication.

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

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

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

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

21 DR. ALLEN: I would.

22 DR. GILSTRAP: I think that is an excellent point  
23 because you are supposed to pull with a perpendicular plane  
24 and not rock or use torque. So I agree. That is a good  
25 point.

1 DR. BLANCO: Anybody have a problem with moving  
2 them up to contraindications? It doesn't seem so so we  
3 would suggest that they get moved up.

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

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

17 Larry, did you have a comment?

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

25 DR. BLANCO: The other way to look at it is the

1 shoulder dystocia--I guess there are two ways. You could  
2 say, "Well, if you didn't use the vacuum, you may not have  
3 delivered vaginally and you wouldn't have gotten the  
4 shoulder." But, at the same time, is the shoulder really  
5 related as a complication of the vacuum or is it a  
6 complication of the fact that you have got too big a baby or  
7 it is not presenting to the pelvis appropriate.

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

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

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

18 DR. ROY: And what about infection?

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

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

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

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

25 DR. MITCHELL: That was in relation to a scalp

1 injury. A scalp injury could then develop infection. That  
2 is how that came about.

3 DR. BLANCO: We have got scalp injury.

4 DR. GILSTRAP: It is already covered; right.

5 DR. BLANCO: That is sort of a secondary event.

6 The scalp injury is what the vacuum might do and then it  
7 might get infected or it might not. And that may be  
8 influenced by the care the neonate receives afterwards not  
9 so much the procedure, itself. You may want to have some  
10 statement about the shoulder but not that it is a direct  
11 adverse effect but that, in patients where--something to the  
12 effect that patients who have instrumented deliveries may  
13 have a higher rate of shoulder dystocia so you should be  
14 aware--or maybe just more like a notice and awareness that  
15 you may have a higher rate of shoulder dystocia in patients  
16 who had an instrumented vaginal delivery.

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

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

24 DR. BLANCO: Anything else on any of these--

25 DR. GILSTRAP: Still fetal, or both?

1 DR. BLANCO: Whichever. Shall we move over to  
2 maternal?

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

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

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

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

19 MS. YOUNG: I was going to sort of raise the issue  
20 of the timing of information. Would it not be appropriate  
21 for the woman, before she goes into labor, sometimes during  
22 her pregnancy, for her to be given some information about  
23 benefits and risks of this procedure along with benefits and  
24 risks of Caesarian section and other procedures as well.

25 I think the timing here--

1 DR. BLANCO: Let me tell you as I would see it.  
2 Again, this goes back to the regulatory issue of FDA; we are  
3 trying to regulate the device and make sure it is safe and  
4 effective. Essentially, if that gets put into the  
5 requirement, almost every woman, during her prenatal care,  
6 would need to have some education about the vacuum whether  
7 she ever has a vacuum or not.

8 The vacuum is still--it is only, what, 5.9 percent  
9 and everyone would have--how would you know who you were  
10 going to use it on before you get to the situation where you  
11 are going to use it?

12 MS. YOUNG: I realize that. When can the risks  
13 be--I think that we need to have--I guess I have a problem  
14 with "as time permits," because that is a sort of vague  
15 wording. Somebody could always say, "Yeah; well, there  
16 wasn't enough time."

17 I would prefer to see that the patient be informed  
18 of the risks and just not put the proviso in there, "as time  
19 permits."

20 MS. SHARTS-HOPKO: Diony, you are in an emergent  
21 situation when this is going on. My observation is most of  
22 the time people say, "Look; this is what I need to do and  
23 this is why." But that is the time they had to say that.

24 DR. GILSTRAP: I think "as time permits" covers it  
25 because, as time permits, you might do it in a prenatal--in

1 your office. You may cover all those things if you want to.  
2 I cover those things. But, as you know, in certain patient  
3 populations that we have dealt with, you don't have time.  
4 They come in and they weren't seen prenatally.

5 You are not given that opportunity and then you  
6 discover they are bradycardic and the head is sitting there  
7 and you don't have time to go through all of that. So, "as  
8 time permits" does cover all of that. It is purposely vague  
9 and it is good.

10 MS. YOUNG: Too vague for me.

11 DR. BLANCO: Other members.

12 DR. ROY: I sort of like it. I have been  
13 persuaded that "as time permits" can really give you the  
14 flexibility to do the antepartum education if you choose to  
15 do it and have the occasion to do it. But, in advance of  
16 having to do it acutely, you explain to the patient in a few  
17 words what is going on and what needs to be done. You do it  
18 and you go with it.

19 MS. SHARTS-HOPKO: I also think good prenatal  
20 education covers that occurrence, forceps, Caesarian  
21 section, a trot through the NICU, those kinds of things.

22 MS. YOUNG: It should.

23 MS. SHARTS-HOPKO: Yes.

24 DR. BLANCO: But, again, I would point, I think in  
25 the overall population, it is about 8 percent. But, in

1 certain areas, like where he and I used to work, it is much  
2 higher than that and you are not going to be able to cover  
3 it prenatally.

4 MS. YOUNG: Just looking at that "as time  
5 permits," again, could one say something like "whenever  
6 possible," or, "in all possible situations," the patient  
7 should be apprised.

8 DR. GILSTRAP: But it is always possible. You  
9 could not effect the emergent delivery. You could take the  
10 time to go through all of that as the baby's heart rate is  
11 down. "As time permits," I think, covers that better. If  
12 the baby is bradycardic and the heart rate is 70, you don't  
13 have time to go through and say, "Here is what a subgaleal  
14 bleed is and a hematoma. Here is what this is. Here is  
15 what that is."

16 You have to say, "I need to get your baby out now.  
17 The quickest, best way I can is to use this instrument."

18 DR. BLANCO: I think Ms. Young's objection is  
19 noted but I think the majority of the panel probably would  
20 like to see "as time permits."

21 Moving right along, as promised. Now we are  
22 really on No. 4 which is prerequisite information for a  
23 vacuum-assisted delivery. Actually, it is not exactly  
24 equivalent but I think it is probably additive. If it is  
25 redundant, some of it may be taken out but probably we need

1 to look at both.

2 Any comments?

3 DR. GILSTRAP: No. 3; I would just use the same  
4 terminology and put "knowledge of the station, position and  
5 attitude of the fetal head," as precisely as possible. The  
6 American College uses that same terminology and I am trying  
7 to get them to change it, also. Just to say "knowledge of  
8 the station, position and attitude." Hopefully, it is the  
9 best you can do anyhow. I don't know why we put that one  
10 caveat in there in that part.

11 DR. BLANCO: Anything else? Again, here, we got  
12 the no demonstrable CPD which I think we have said, three  
13 different times in three different places. So I don't know  
14 whether we need to have it everywhere. Maybe it is  
15 important enough that it needs to be in more than one place.  
16 But that is the other thing.

17 We did change it to fetal pelvic disproportion so  
18 we probably ought to change it here as well if we are going  
19 to leave it in here.

20 Any other problems with the five items on the  
21 left? If not, let's proceed to the items on the right.  
22 Engage fetal head; knowledge of the station, position and  
23 attitude of the fetal head. Actually, Dr. Gilstrap, maybe  
24 putting a proviso in there might be good because you say,  
25 "knowledge of the station, position and attitude of the

1 fetal head," that means if you--say, you have a lot of  
2 caput. Should you then not apply the vacuum because you are  
3 not certain of where the occiput and where the sutures are?  
4 I am just playing the devil's advocate.

5 DR. GILSTRAP: I don't think you ought to put it  
6 on if you don't know the exact position of the head. I  
7 think that is where you get in trouble because if you have  
8 so much caput and you put it on too far anteriorly, you get  
9 extension of the head, that is a setup. That is a risk that  
10 I don't think you ought to be taking with a woman's baby.

11 DR. BLANCO: So then it should specifically say,  
12 "knowledge of the station, position and attitude of the  
13 fetal head."

14 DR. GILSTRAP: You could be wrong. You could feel  
15 a posterior fontanelle and think it is anterior. We have  
16 all done that.

17 DR. BLANCO: Sure.

18 DR. GILSTRAP: I mean, to the best of your  
19 knowledge of the head.

20 DR. BLANCO: I think the implication is--I think  
21 that some people have said, "Well, vacuum is safe so even if  
22 I don't know exactly where the occiput is, if I get it close  
23 by, I am going to be okay." I think what we are saying is,  
24 "That is not good enough. We really do want you to put it  
25 in the exact position."

1 DR. GILSTRAP: Absolutely.

2 DR. BLANCO: So we do want to know where that  
3 occiput is; right?

4 DR. GILSTRAP: Yes.

5 DR. BLANCO: Adequate anesthesia. I think we have  
6 already addressed the experienced operator or supervisor.  
7 Capability of performing a Caesarian section. Willingness  
8 to abandon the procedure. That might be a little general  
9 for folks. But I think it is necessary. You have got to be  
10 able to throw in the towel and say, "Okay; it is time to go  
11 another route."

12 I don't know if you want to word that any  
13 differently.

14 DR. GILSTRAP: I like it and I think it is very  
15 important. It is the same concept we had with forceps.  
16 This is not--you don't get a trophy for getting the baby out  
17 this way.

18 DR. BLANCO: So be it. Knowledge of the mechanism  
19 of labor by the operator. Knowledge of the actual course of  
20 labor or the patient who requires the vacuum-assisted  
21 delivery. Empty bladder. Term or near-term infant. No  
22 demonstrable clinical cephalopelvic disproportion. That is,  
23 I think, about the fifth time we have heard that one and we  
24 have changed it to fetal. And then, neonatal resuscitation  
25 expertise available.

1 MS. YOUNG: Can I ask a question about the last  
2 one, neonatal resuscitation. It occurred to me, what about  
3 a small community, rural hospital, where you have a family  
4 practitioner who is doing this delivery and is using this  
5 procedure. What does he or she need to have available in  
6 terms of neonatal resuscitation and what is the availability  
7 in terms of a small, rural hospital?

8 DR. GILSTRAP: Probably bag and mask. That is  
9 resuscitation.

10 MS. YOUNG: You are not talking about a person,  
11 then.

12 DR. GILSTRAP: Someone that knows how to use a bag  
13 and a mask to ventilate a baby and not to do it too much.  
14 That is a relatively easy skill to teach. All of our  
15 midwives do that and our family-practice physicians do that.

16 DR. BLANCO: I think what Ms. Young is bringing up  
17 is even broader. It is the issue is there a community  
18 standard where some rural, small hospitals may have certain  
19 things available and not others or is there a national  
20 standard that, at your place, a high-powered institution, is  
21 going to be there.

22 I think, in this day and age, it is pretty much a  
23 community standard. The hospital has to meet standards or  
24 they shouldn't be delivering babies, putting themselves in  
25 this position. But I think the neonatal resuscitation would

1 simply be someone with the ability to bag and mask the baby  
2 and provide oxygen, as Dr. Gilstrap says.

3 DR. GILSTRAP: Or we could say someone with  
4 "basic" instead of "advanced," where you have to be able to  
5 put a tube in.

6 MS. YOUNG: Okay.

7 DR. BLANCO: Any comments? Anybody?

8 MS. YOUNG: Is that any different from any other  
9 delivery? If you need neonatal resuscitation, you need  
10 neonatal resuscitation wherever they are delivered. Is it  
11 unique to those who are delivered by vacuum assistance?

12 DR. BLANCO: No; I think your point is well taken.

13 DR. CHATMAN: It can't be different in rural Iowa  
14 than it is in New York.

15 DR. BLANCO: I would hope not.

16 DR. GILSTRAP: That is a good point. Why don't we  
17 just leave it off. Good point. Excellent.

18 DR. BLANCO: Somebody brings up the point of home  
19 deliveries. I hope nobody--first of all, I don't even want  
20 to comment on home deliveries, but home deliveries with a  
21 vacuum extraction?

22 MS. YOUNG: No, no.

23 DR. BLANCO: I don't know about that.

24 MS. YOUNG: I am not aware that any have been  
25 done.

1 DR. BLANCO: Let's open up the meeting maybe for  
2 about ten minutes or so, seven minutes or so, to the public.

3 DR. MITCHELL: I'm sorry; after prerequisites,  
4 there is the directions for use.

5 DR. BLANCO: Oh; you mean I missed something here?

6 DR. MITCHELL: Persisting with delivery,  
7 discontinuation of the delivery.

8 DR. BLANCO: I don't know if I am going to allow  
9 you to slip that one by us, Dr. Mitchell. It is not on the  
10 question here.

11 DR. MITCHELL: It was under the clinician use  
12 information question.

13 DR. BLANCO: All right. Well, we will let you  
14 slip it in, then. Here we go. Preparation, use of the  
15 fetal vacuum extractor for assisted vaginal delivery and  
16 placement under the fetal head.

17 DR. MITCHELL: That is only two of four overheads.

18 DR. BLANCO: Okay. Thank you for pointing that  
19 out.

20 DR. ROY: Seems okay to me.

21 DR. BLANCO: The only thing I would say is that  
22 one on the left is somewhat redundant of some of the things  
23 we have already said in the second sentence. And the first  
24 sentence may actually be somewhat device driven. Some of  
25 the devices may be a little different. I think that may

at

1 also apply to the right.

2           So maybe what we can say is that, in general, they  
3 should have some description of the device-specific way in  
4 which it should be utilized and where it should be place on  
5 the head. How does the panel feel about that? You can use  
6 this statement as a guide for the amount of information that  
7 needs to be provided. Okay? Any problem?

8           Let's move on. There is a fourth. Bring it on.

9           DR. MITCHELL: Again, I think the issues that I  
10 want to address specifically are underlined and then the  
11 first check mark on the second one.

12           DR. BLANCO: We would love to comment on all that  
13 you put before us, Dr. Mitchell.

14           DR. ALLEN: Again, with the pull and  
15 synchronization, I would put, "with the contraction or  
16 maternal expulsive efforts."

17           DR. BLANCO: And the XXX, again; that may be  
18 device specific. If not, some places should state how that  
19 level was arrived at.

20           DR. ALLEN: If the cup starts to come off--I don't  
21 know if we should encourage--if it is coming off for a  
22 reason, perhaps we should just let it come off rather than  
23 keeping the vacuum intact.

24           DR. BLANCO: What would you do, though, if you  
25 feel like it is going to come off? Would you rather stop

1 and recheck?

2 DR. ALLEN: Yes.

3 DR. BLANCO: But that is not just letting it come  
4 off. So maybe instead of saying what to do, you should say,  
5 "if it starts to come off, you should try to maintain it on,  
6 and recheck application."

7 DR. CHATMAN: If it starts to come off, reevaluate  
8 the--

9 DR. BLANCO: Yes; I think we need to add that  
10 because that is when you get a--usually, when you put it on  
11 and you feel all around, you make sure there is no maternal  
12 tissue, the way you get maternal tissue in is you pull on it  
13 and it starts to come off and you get a little maternal  
14 tissue in there. So I would add that, make sure there is no  
15 maternal tissue.

16 But how do you want it reworded, the second part  
17 of that sentence, or do you want to give some guidelines if  
18 it starts to come off?

19 DR. CHATMAN: Reevaluate the application?

20 DR. BLANCO: Okay; sounds fine. I think Dr.  
21 Gilstrap mentioned this when we were talking about--I don't  
22 know if it was contraindications or warnings--if you don't  
23 get descent, you probably better quit. You are not going to  
24 get a benefit out of the procedure. So I think that is  
25 important to put in there.

1 DR. ROY: Should that be highlighted in some way  
2 as opposed to the rest of the instructions?

3 DR. BLANCO: I think, again, as Dr. Gilstrap  
4 pointed out, you shouldn't feel like you are going to get a  
5 medal or a trophy for doing this to the point that you are  
6 going to get the patient to deliver vaginally. So it is  
7 probably an important concept.

8 Do we want to move it up? Remember the severity  
9 is contraindication, warnings, precautions and directions  
10 for use. Do we want to move it up in our concern list?

11 DR. MITCHELL: It is listed elsewhere.

12 DR. BLANCO: Is it?

13 DR. MITCHELL: Yes.

14 DR. BLANCO: At what level? Do you remember? As  
15 a warning--it is not a contraindication. So it must be a  
16 precaution or a warning; right?

17 DR. ALLEN: Yes.

18 DR. BLANCO: Is that okay with the panel?

19 MS. DOMECUS: You can also, in this section, just  
20 put a box around it, italicize it or bold it or something if  
21 you want it to stand out from the long list of directions  
22 for use.

23 DR. BLANCO: Okay.

24 DR. ROY: Italicize it or do something so that it  
25 jumps out at you.

1 MS. DOMECUS: Yes.

2 DR. BLANCO: Any other comments on any of this?  
3 Do you have anything else you would like for us to comment  
4 on, Dr. Mitchell?

5 DR. MITCHELL: Thank you very much. Those were  
6 the last two.

7 DR. BLANCO: Let's have a few moments of public  
8 discussion. Is there anyone in the public that would like  
9 to address this, address the panel, or address any issues?  
10 Please remember to identify yourself, your connection and  
11 conflict of interest.

12 MS. BILTZ: Tracy Biltz, Director of Medical  
13 Products with Prism Mityvac. I just wanted to, again,  
14 address our esteemed panel and all of the members here today  
15 to give you a little bit of background. That was a lot of  
16 discussion as to where did some of this information come  
17 from.

18 Clearly, as the originators of the product and as  
19 leaders in the marketplace, a lot of this stuff did come  
20 from our company. So let me just kind of give you some  
21 information as to how it got here.

22 First of all, I noted that it was difficult and,  
23 many times, challenging for us to define what is the  
24 definition of X, Y and Z. The reason that I believe that is  
25 because we are dealing with things that are normative

1 practice behavior standards versus evidence-based research  
2 prospective randomized studies.

3           What has evolved over the course of many years in  
4 the studies that we saw; as you saw the injuries ramping up,  
5 you all see usage of vacuum extraction ramping up. So you  
6 saw the converse happening with forceps. So there you see  
7 at least some explanation as to why you will see increased  
8 incidence. You have seen significantly larger uses of  
9 vacuum extractions especially in the teaching facilities.

10           There is actually a study by Dr. Bofill that cites  
11 the use of vacuum extraction being much greater in residents  
12 or physicians that were trained in the last ten years than  
13 those that were trained ten to twenty years ago.

14           I agree with most things that we stated here  
15 today. Just to give you at least some comment on, "Do not  
16 allow the vacuum to remain at maximum levels for ten  
17 minutes." Ten minutes is conservative. Obviously, we do  
18 have some attorneys that advise us. If you look in the  
19 research, you will see anything from ten to twenty minutes.

20           Dr. Bofill had twenty. That is accrued vacuum.  
21 Attorneys, obviously, are going to advise us, as a  
22 manufacturer, to be very conservative. So we chose ten  
23 minutes. And that is where that came from. So we would,  
24 obviously, and the clinicians would, prefer that that number  
25 be moved.

1 But that is not based on a prospective, randomized  
2 study. It is normative practice, accepted guidelines.

3 Additionally, with the three popoffs. Again, it  
4 is an arbitrary empirical number that has been designated,  
5 again not truly that has been researched.

6 Another point that I did want to raise that we  
7 didn't discuss was underneath, on warnings and precautions,  
8 No. 4, there is a bullet point; vacuum pressure should be  
9 reduced between contractions.

10 DR. BLANCO: I'm sorry; let me interrupt you for a  
11 second--not what you are saying. Somebody is passing this  
12 along to have all the consultants' addresses and E-mails.  
13 We can do that. Please go ahead. I'm sorry for the  
14 interruption.

15 MS. BILTZ: No problem. Vacuum pressure should be  
16 reduced between contractions to reduce the possibility of  
17 trauma to the neonatal scalp. There is a research study  
18 that was done by, again, Dr. Bofill. They had about 500  
19 deliveries where they did not see any complications with the  
20 baby's head and they left the vacuum intact throughout the  
21 procedure. They did not reduce the vacuum.

22 So there is at least a study that addresses that  
23 and we might want to look at that before we make this  
24 recommendation.

25 My only other comment and then I will allow

1 someone else to speak is that the primary reason I raised  
2 the issue of Caesarian section is it is very much like some  
3 of the things that we discussed today. Where did the ten  
4 minutes accrue from, the three popoffs? Those things came  
5 because our clinicians needed guidance and they wanted to  
6 know what is happening across the nation and internationally  
7 with the use of this product.

8           We can't go to evidence-based data but we need to  
9 know what other clinicians are doing. That was from market  
10 surveys and from information that we have gleaned over  
11 twenty years of experience.

12           In the same regard, the use of vacuum extraction  
13 with about 5 to 7 percent of Caesarian sections. That is,  
14 again, from an analysis of how the product is being used and  
15 that is primarily our job is to find out how it is being  
16 used and then to try to determine how it should best be  
17 used.

18           So I hope that at least that gives you some  
19 information as to how this information has been developed.  
20 Thank you.

21           DR. BLANCO: Thank you very much. We appreciate  
22 your comments. Is there anyone else from the public or  
23 industry that would like to make a comment?

24           DR. VACCA: I am Aldo Vacca. I am an obstetrician  
25 from Brisbane in Australia. I would like to thank you for

1 the opportunity to speak and say how much I have enjoyed  
2 listening to the deliberations. I have one or two things I  
3 would like to comment on.

4           Firstly, no one has mentioned the Cochran Library  
5 database where there is the best available evidence for many  
6 of the questions that were raised here. I would suggest, if  
7 I may, that that is consulted and, particularly, the  
8 individual randomized controlled trials that were done  
9 there.

10           I was interested in Dr. Mitchell's paper that she  
11 didn't list as one of her recommendations, the training,  
12 because I think this is one of the crucial issues that needs  
13 to be addressed. I have some concern when we raised the  
14 issue of maternal exhaustion, lack of cooperation, excessive  
15 analgesia, inadequate contractions, and so on, as a major  
16 indication for vacuum extraction.

17           You must realize that you are running the risk of  
18 increasing the subgaleal hemorrhages because you are going  
19 to increase the traction force. My view would be, first of  
20 all, to increase--use other agents such as Pitocin to  
21 increase these and you will find--I have found that often  
22 the exhaustion is more psychological than physical.

23           I think we really should address those issues. It  
24 is a real worry. I think one needs to be very careful when  
25 we say maternal exhaustion because you run the risk of

1 increasing the injuries that you are trying to prevent.

2 I never, in the thirty years that I have been  
3 using the Malmstrom and then the Bird cups, the metal cups,  
4 I have never, ever reduced the pressure in between the  
5 contractions. I believe there is no evidence, whatsoever,  
6 and now we have got some randomized controlled evidence,  
7 that there is no benefit to be gained by doing this.

8 In fact, it may be distracting as we have  
9 commented on here. In my own hands and in my resident's I  
10 get concerned if there is one popoff. I do not, and I agree  
11 with Dr. Gilstrap, see that as a safety mechanism. There is  
12 a reason for popoff and, in my opinion, the vast majority  
13 can be prevented with correct technique.

14 I do think sudden popoffs are abrasive and, if we  
15 want to reduce many of the superficial scalp injuries then  
16 we should be preventing popoffs.

17 I would like to conclude in that I believe that  
18 every vacuum extraction should be audited. I do that in my  
19 unit. There should be feedback so that we know where we are  
20 going wrong. Many of the issues that were raised here would  
21 be addressed with proper auditing.

22 The final question I would like to raise is  
23 maternal counseling. I believe, as Dr. Young said, that  
24 there should be prenatal discussions about vacuum  
25 extraction. In my unit, we actually have the midwives

1 incorporating a prenatal discussion or format that I have  
2 produced. This is actually discussed in the prenatal  
3 classes.

4 I have produced a CD ROM in which case there is a  
5 section specifically devoted for the education and  
6 information of mothers and others. I dare say that many of  
7 us here are "others" as well. I have on the Internet an  
8 abridged version of this where people can access it for  
9 themselves.

10 I do believe there should be a general awareness  
11 of vacuum extraction for the people on whom we actually  
12 perform this instrumentation.

13 Once again, thank you for having me.

14 DR. BLANCO: Thank you for your comments. Any  
15 other public or industry comment? If not, Dr. Roy, did you  
16 want to make a comment?

17 DR. ROY: No. I just wanted to ask--he gave us  
18 his thirty years experience. How long do you leave the  
19 vacuum on?

20 DR. VACCA: I was pleased to hear that we  
21 concluded that there shouldn't be a time limit. I am  
22 answering your question in a roundabout fashion. Most  
23 vacuum extractions are completed within five to nine  
24 minutes. I would say that fifteen minutes is of no  
25 consequence.

1           It is not what happens while a cup is attached to  
2 the head. It is what you do afterwards. So I think there  
3 are traction forces and we heard about physics and so on  
4 before. I think there are more factors involved. Ten to  
5 fifteen minutes, I have no problem with that.

6           DR. BLANCO: Thank you. Dr. Yin or Mr. Pollard,  
7 would you like some parting comments from the FDA?

8           DR. YIN: Again, I want to thank the panel. This  
9 is really a very, very good serious discussion and we need  
10 it badly. I want to thank our Chairperson, again, Dr.  
11 Blanco. Every little thing is discussed. Nothing has been  
12 skipped. So I do thank you. I think we thank Dr. Gilstrap  
13 that is so willing to help us out and especially all the  
14 manufacturers.

15           Yes; we agree. We did use ACOG's and all the  
16 companies to come up with this list. So it is very long.  
17 You know that we should not be blamed. Thank you all.  
18 Special thanks to the panel, the companies and our FDA  
19 staff. They worked very hard.

20           DR. BLANCO: Any comments, replies, from the panel  
21 members?

22           MS. YOUNG: May I just make a comment. I was  
23 going to do this before we went to the second open session  
24 on the template. I notice that only one reference is listed  
25 under No. 10 and that is an ACOG Technical Bulletin from

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

at

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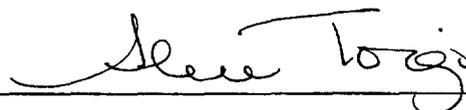
1 and I want to thank all of the FDA staff for their wonderful  
2 support, Mr. Pollard, Dr. Yin, Dr. Harvey. Everyone else  
3 that presented and that was included did a great job. We  
4 appreciate it.

5 Thank you very much and, unless someone else has  
6 something else, we stand adjourned.

7 [Whereupon, at 4 o'clock p.m., the meeting was  
8 adjourned.]

**C E R T I F I C A T E**

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written above a horizontal line.

**ALICE TOIGO**