

UNITED STATES OF AMERICA  
 DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 CENTER FOR DEVICES AND RADIOLOGIC HEALTH  
 OBSTETRICS AND GYNECOLOGY DEVICES PANEL  
 SEVENTY-THIRD MEETING  
 OPEN SESSION

FRIDAY, DECEMBER 14, 2007

The meeting came to order at 9:20 a.m. in the Grand Ballroom of the Hilton Washington DC North, 620 Perry Parkway, Gaithersburg, MD. Dr. Marcelle Cedars, MD, Chair, presiding.

PRESENT:

MARCELLE CEDARS, MD	ACTING PANEL CHAIR
DIANA ROMERO, PHD, MA	CONSUMER REP.
ELISABETH GEORGE	INDUSTRY REP.
PAULA HILLARD, MD	VOTING MEMBER
HOWARD SHARP, MD	VOTING MEMBER
ANN DAVIS, MD	CONSULTANT
MELISSA GILLIAM, MD, MPH	CONSULTANT
HERBERT PETERSON, MD	CONSULTANT
KATHLEEN PROPERT, SCD	CONSULTANT
SUSAN RAMIN, MD	CONSULTANT
NANCY SHARTS-HOPKO, RN, PHD	CONSULTANT
RUSSELL SNYDER, MD	CONSULTANT
PHILLIP STUBBLEFIELD, MD	CONSULTANT
RICHARD ZAINO, MD	CONSULTANT
MICHAEL T. BAILEY, PHD	EX. SEC.
ELAINE BLYSKUN	INCOMING EX. SEC.
NANCY BROGDON	FDA

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

## T-A-B-L-E O-F C-O-N-T-E-N-T-S

Open Session Call to Order, Dr. Marcelle Cedars.....	3
Introductory Remarks, Colin Pollard, Chief, Obstetrics and Gynecology Devices Panel.....	13
Post-Approval Study Update, Danica Marinac-Dabic, M.D., Ph.D., Chief, Epidemiology Branch.....	14
Post-Approval Presentation - InSightec, Inc., ExAblate 2000 System.....	33
FDA Presentation.....	46
Questions From Panel.....	63
FDA Presentation - Endometrial Ablation...	77
Open Public Hearing Session	
Arthur McCausland.....	104
Ellen Sheets.....	115
Seth Stabinsky.....	123
Todd Sloan.....	127
FDA Questions:	
1 - Ethical Principles.....	130
2 - Study Design.....	171
3 - Study Inclusion/Exclusion Criteria..	186
9 - Risk of Masking Uterine Cancer.....	204
7 - Questionnaires.....	206
8 - Rate of Adverse Events.....	208

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

P-R-O-C-E-E-D-I-N-G-S

9:20 a.m.

CHAIR CEDARS: I would like to call this meeting of the Obstetrics and Gynecology Devices Panel to order. I'm Dr. Marcelle Cedars, the Chair for this panel. I am a reproductive endocrinologist, Director of the Division of Reproductive Endocrinology and Vice Chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at UCSF.

If you haven't already done so, please sign the attendance sheets that are on the table by the doors. If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do so with Karen Oliver.

Karen. Thank you.

No one from the public or the press is allowed into the panel area at any time during the break or during the conduct of this meeting. I would like to ask everyone to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 please silence their cell phones and other  
2 electronic devices.

3 Dr. Bailey, the Executive Secretary  
4 for the Obstetrics and Gynecology Devices  
5 Panel, will make some introductory remarks.

6 DR. BAILEY: The first thing I will  
7 do is I will read the conflict of interest  
8 statement.

9 The Food and Drug Administration is  
10 convening today's meeting of the Obstetrics  
11 and Gynecology Devices Panel of the Medical  
12 Devices Advisory Committee under the authority  
13 of the Federal Advisory Committee Act of 1972.

14 With the exception of the industry  
15 representative all members and consultants of  
16 the panel are special Government employees or  
17 regular federal employees from other agencies  
18 and are subject to federal conflict of  
19 interest laws and regulations.

20 The following information on the  
21 status of this panel in compliance with  
22 federal ethics and conflict of interest laws

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 covered by but not limited to those found at  
2 18 USC 208 and 712 of the Federal Food, Drug,  
3 and Cosmetic Act are being provided to  
4 participants in today's meeting and to the  
5 public.

6 FDA has determined that members and  
7 consultants of this panel are in compliance  
8 with federal ethics and conflict of interest  
9 laws under 18 USC 208. Congress has  
10 authorized FDA to grant waivers to special  
11 Government employees who have potential  
12 financial conflicts when it is determined that  
13 the agency's need for a particular individual  
14 service outweighs his or her potential  
15 financial conflict of interest under 712 of  
16 the FDNC Act.

17 Congress has authorized FDA to  
18 grant waiver to special Government employees  
19 and regular Government employees with  
20 potential financial conflicts when necessary  
21 to afford the committee essential expertise.

22 Related to the discussion of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 today's meeting members and consultants of the  
2 panel who are special Government employees  
3 have been screened for potential financial  
4 conflicts of interest of their own as well as  
5 those imputed to them including those of their  
6 spouses or minor children and for purposes of  
7 18 USC 208 their employers. These interests  
8 may include investments, consulting, expert  
9 witness testimony, contacts, grants, teaching,  
10 speaking, writing, patents and royalties and  
11 primary employment.

12 Today's agenda involves a  
13 post-approval study update for Exablate 2000  
14 system from InSightec, Inc. The system is  
15 indicated for ablation of uterine fibroid  
16 tissue in pre or post-menopausal women with  
17 symptomatic uterine fibroids who desire  
18 uterine-sparing procedure.

19 In addition, the panel will have a  
20 general topic discussion of clinical trial  
21 design issues for endometrial ablation devices  
22 indicated for premenopausal women for whom

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 childbearing is complete and who no longer  
2 desire menses.

3           Based on the agenda for today's  
4 meeting and all financial interest reported by  
5 the panel members and consultants, no conflict  
6 of interest waivers have been issued in  
7 connection with this meeting. A copy of the  
8 statement will be available for review at the  
9 registration table during the meeting and will  
10 be included as part of the official  
11 transcript.

12           Elisabeth George is serving an  
13 industry representative acting on behalf of  
14 all related industry and is employed by  
15 Phillips Medical System. We would like to  
16 remind members and consultants that if  
17 discussions involve any other products or  
18 firms not already on the agenda for which an  
19 FDA participant has a personal or imputed  
20 financial interest, the participants need to  
21 exclude themselves from such involvement and  
22 their exclusion will be noted for the record.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 FDA encourages all other participants to  
2 advise the panel of any financial  
3 relationships they may have with any firms at  
4 issue. Thank you.

5 Before I turn the meeting back to  
6 Dr. Cedars, I wanted to just read a couple of  
7 additional statements. Transcripts of today's  
8 meeting are available from Neal Gross and  
9 Company. Information on purchasing videos of  
10 today's meeting can be found at the table  
11 outside the meeting room.

12 Presenters to the panel who have  
13 not already done so should provide FDA with a  
14 hardcopy of their remarks including overheads.

15 If you have slide presentations that you  
16 would like to load onto our computer, we have  
17 pointed out Karen Oliver but we will have a  
18 break here in the morning I think before the  
19 open public hearing and you can talk with  
20 Karen at that time to get them loaded.

21 I would like to remind everyone  
22 that members of the public and the press are

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 not permitted around the panel area beyond the  
2 speaker's podium. The press contact for  
3 today's meeting is Peper Long in the back.  
4 Wave at everybody, Peper.

5 I request the reporters wait to  
6 speak to FDA officials until after the panel  
7 meeting. I will now pass it back to Dr.  
8 Cedars.

9 CHAIR CEDARS: Before we begin I  
10 would like to ask our panel members who are  
11 generously giving their time today and other  
12 FDA staff seated at this table to introduce  
13 themselves. Please state your name, your area  
14 of expertise, your position, and affiliation.

15 Dr. Snyder.

16 DR. SNYDER: Russell Snyder. I'm a  
17 general OB-GYN, Division Director of  
18 Gynecology, University of Texas Medical Branch  
19 at Galveston.

20 DR. STUBBLEFIELD: Phillip  
21 Stubblefield. I'm Professor of Obstetrics and  
22 Gynecology at Boston University, Boston

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Medical Center. I have a long-term interest  
2 in contraception.

3 DR. ZAINO: I'm Richard Zaino. I'm  
4 a gynecologic pathologist and professor of  
5 pathology at Penn State Milton S. Hershey  
6 Medical Center in Hershey, Pennsylvania.

7 DR. RAMIN: I'm Susan Ramin. I'm  
8 Professor and Chair of the Department of  
9 Obstetrics, Gynecology and Reproductive  
10 Sciences at the University of Texas Medical  
11 School of Houston. My specialty is maternal  
12 fetal medicine.

13 DR. DAVIS: I'm Anne Davis. I'm  
14 Director of Pediatric, Adolescent, and Young  
15 Adult Gynecology at Tufts University School of  
16 Medicine.

17 DR. SHARTS-HOPKO: I'm Nancy  
18 Sharts-Hopko. I'm Director of the Ph.D.  
19 program in the College of Nursing at Villa  
20 Nova University and I'm a women's health  
21 nurse.

22 MS. BLYSKUN: I'm Elaine Blyskun

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 and I'm the incoming Executive Secretary of  
2 the OB-GYN Devices Panel.

3 DR. BAILEY: Mike Bailey, Exec.  
4 Sec. of the OB-GYN Devices Panel.

5 DR. SHARP: Howard Sharp. I'm a  
6 OB-GYN University of Utah School of Medicine  
7 and Vice Chair for Clinical Affairs.

8 DR. PETERSON: Herbert Peterson.  
9 I'm an OB- GYN Epidemiologist. I'm the Chair  
10 and Professor in the Department of Maternal  
11 and Child Health at the University of North  
12 Carolina and also a Professor in the  
13 Department of Obstetrics and Gynecology.

14 DR. PROPERT: Kathleen Propert.  
15 I'm a Professor of Biostatistics at the  
16 University of Pennsylvania specializing in  
17 clinical trials.

18 DR. GILLIAM: Melissa Gilliam. I'm  
19 an Associate Professor in the Department of  
20 Obstetrics and Gynecology at the University of  
21 Chicago and Division Director of Family  
22 Planning.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. HILLARD: Paula Hillard. I'm  
2 Professor of Obstetrics and Gynecology and  
3 Chief of the Division of Gynecologic  
4 Specialties at Stanford University School of  
5 Medicine and I do adolescent pediatric  
6 gynecology.

7 MR. GEORGE: Elisabeth George, Vice  
8 President of Quality and Regulatory at  
9 Phillips Medical Systems.

10 DR. ROMERO: Diana Romero,  
11 Associate Professor of Urban Public Health  
12 City University of New York and also in the  
13 Department of Population and Family Health at  
14 Columbia University.

15 MS. BROGDON: I'm Nancy Brogdon.  
16 I'm not a member of the panel. I'm the  
17 Director of FDA's Division of Reproductive  
18 Abdominal and Radiological Devices.

19 CHAIR CEDARS: Thank you. Next  
20 Colin Pollard who is Chief of the Obstetrics  
21 and gynecology Devices Branch would like to  
22 make some introductory comments to the panel.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           MR. POLLARD:       Thank you, Dr.  
2 Cedars.    My comments will be very brief.  
3 First of all, I just wanted to echo your  
4 comments a minute ago about our appreciation  
5 of the generous giving of the time of the  
6 entire panel to come out here.   I want to  
7 especially thank you for your hard work and  
8 deliberations yesterday on a difficult topic.  
9       We truly do appreciate all of that.

10           This morning we basically have two  
11 agenda items for you and I'm just going to  
12 very briefly introduce them and we'll just get  
13 right to it.   We are going to apprise the  
14 panel about one post-approval study experience  
15 from a PMA we approved a few years ago and let  
16 you know what's going on with that.

17           After that we are going to  
18 introduce a general topic in the area of  
19 endometrial ablation and the use of that  
20 electively for what we call a lifestyle  
21 indication and ask the panel to help us look  
22 at that topic and any clinical trial that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 might be done in that area. Thank you.

2 CHAIR CEDARS: Thank you. We are  
3 now going to hear an update on post-approval  
4 studies for devices in Obstetrics and  
5 Gynecology Devices Branch by Dr. Danica  
6 Marinac-Dabic, Chief of Epidemiology in the  
7 Office of Surveillance and Biometrics.

8 Dr. Marinac-Dabic.

9 DR. MARINAC-DABIC: Good morning,  
10 ladies and gentlemen, Madam Chair,  
11 distinguished members of the panel. My name  
12 is Danica Marinac- Dabic. I'm the Chief of  
13 Epidemiology Branch at the Office of  
14 Surveillance and Biometrics which is the unit  
15 that is in charge of the review tracking and  
16 oversight of the post- approval studies  
17 imposed by the PMA order.

18 During the past couple of years the  
19 CDRH has made significant commitment of  
20 resources to enhance the Post-Approval Studies  
21 Program with major goals to enhance scientific  
22 rigor of post-approval studies, to establish

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 and maintain accountability for the  
2 post-approval study commitments, to build  
3 post-approval study information management  
4 system, to build bridge between the  
5 post-market knowledge and the pre-market  
6 device evaluation, and to increase the  
7 transparency with the public.

8 With these goals in mind I am  
9 coming today to you, our expert panel members.

10 We view you as the integral parts of our  
11 review process and to give you an update on  
12 what is happening at the CDRH.

13 First, I would like to talk about  
14 the recent development of the CDRH  
15 Post-Approval Studies Program in general.  
16 Then I will give you a brief overview of the  
17 obstetrics and gynecology post-approval  
18 studies that are currently ongoing.

19 The new CDRH Post-Approval Studies  
20 Program encompasses design, tracking,  
21 oversight, and review responsibilities for the  
22 studies mandated as a condition of approval.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 The program helps ensure that well-designed  
2 post- approval studies are conducted  
3 effectively and efficiently and in the least  
4 burdensome manner.

5 During the last couple of years  
6 CDRH fundamentally changed the processes by  
7 which we handle post-approval studies. No. 1,  
8 we have made changes in the oversight,  
9 tracking, and the review of post-approval  
10 studies.

11 We also issued the guidance  
12 document and developed and released the  
13 post-approval studies webpage. We initiated  
14 post-market updates to the panel and this is  
15 the second of the general updates that has  
16 been given to the panel. The first one I  
17 delivered two weeks ago the Cardiovascular  
18 Devices Panel.

19 We also developed a comprehensive  
20 approach to engage the other public health and  
21 public stakeholders that can help us move  
22 forward in the Post-Approval Studies Program.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           As you may already know, in 2005  
2 the oversight responsibility was transferred  
3 to the Office of Surveillance and Biometrics  
4 from the Office of Device Evaluation. Post-  
5 Approval studies review functions were  
6 integrated into the Medical Device,  
7 Epidemiology and Surveillance Program within  
8 the Epidemiology Branch in OSB.

9           This transfer occurred in two  
10 phases. The initial transfer happened January  
11 1, 2005, and then earlier this year we fully  
12 transferred the program by transferring not  
13 only the oversight but also all review  
14 functions to OSB.

15           We have developed an electronic  
16 tracking system for post-approval study  
17 commitments. This system is based on the  
18 post-approval study time lines that are  
19 incorporated into study protocols and agreed  
20 upon at the time of the approval or shortly  
21 after that.

22           Both the sponsors and the FDA agree

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 on those time lines and according to those  
2 time lines the due dates are set in the  
3 tracking system so every time we can know how  
4 well the sponsors are complying with their  
5 post-market study commitments. This certainly  
6 represents the CDRH determination to ensure  
7 that all post-market commitments are tracked  
8 and fulfilled.

9 The most fundamental changes  
10 occurred at CDRH in the review process of the  
11 PMAs and some of those major changes are  
12 listed on the slide.

13 Over the last two years the  
14 epidemiology staff had been gradually  
15 integrated into the PMA review process. What  
16 that means actually is that when PMA  
17 submission is received by the center and PMA  
18 review team is convened, an epidemiologist is  
19 assigned to each PMA review team.

20 Our goal in those teams is really  
21 to look into post-market issues. Review the  
22 PMA with an eye towards the post-market and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 help the review team to develop the relevant  
2 important post-market questions and then leave  
3 the design of post-approval study with the  
4 sponsor.

5 To advance the least burdensome  
6 approach the epidemiology staff has committed  
7 significant resources to early dialogue with  
8 the manufacturers to give early input  
9 regarding our expectations to identify  
10 post-market questions and to guide the  
11 development of a sound post-market study  
12 design

13 We certainly view that as the least  
14 burdensome manner and we believe that the  
15 sponsor in the long-term will benefit from our  
16 early input so we can work with them as the  
17 pre-market review process is being completed  
18 to also finalize the post-approval study  
19 protocol.

20 The goal is to have that protocol  
21 finalized at the time of the PMA approval.  
22 Sometimes it is not possible. Sometimes we

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 agree only on the outline of the protocol and  
2 then fine tune that protocol very early after  
3 the approval process.

4           Anyhow, the major component of that  
5 work is really accomplished pre-market. The  
6 goal is that we all agree on study time lines  
7 so later when we come to tracking and  
8 monitoring those studies we will be able based  
9 on those time lines to really objectively  
10 assess how well the study is progressing.

11           Certainly when the device goes to  
12 the panel you will see more and more  
13 epidemiologists also presenting as part of the  
14 review team to help the panel understand what  
15 our thoughts are with regard to unanswered  
16 post-market questions and certainly to  
17 stimulate the panel's discussion on the  
18 post-market issues.

19           Again, these were the changes that  
20 happened at the pre-market arena. However,  
21 there were also major changes how we handled  
22 post-market review of the post-approval

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 studies.

2                   Upon the device approval the  
3 epidemiologist assumed the lead responsibility  
4 in the review of the interim and final  
5 reports. The PMA review team, however,  
6 continues to be engaged and informed. This is  
7 accomplished through the establishment of the  
8 post-market review team.

9                   Certainly we have a lead but we  
10 often consult without pre-market colleagues  
11 who are technical experts in the devices and  
12 would help us put some of the findings that we  
13 have in the post-market arena into context.

14                   This whole concept of epidemiology  
15 lead the post-market team availability is  
16 envisioned to couple the epidemiologic  
17 expertise in observational study design with  
18 the product specific technical expertise from  
19 pre-market and post-market experts to  
20 facilitate the pre- market to post-market  
21 knowledge sharing.

22                   Some of you probably already know

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 that we issued the guidance document on  
2 post-approval studies late last year. We had  
3 one minor revision that was issued this year  
4 but we certainly believe that this guidance  
5 will help the sponsors of medical devices to  
6 better understand what the expectations are  
7 and to prepare their reports according to  
8 those expectations.

9 In the guidance documents we  
10 clearly defined what our expectations are in  
11 terms of the reporting status and those are  
12 the definitions of what is considered the  
13 report being on time or overdue. Or if it's  
14 overdue but still received you would like to  
15 give a credit to the sponsor and we make sure  
16 that it is listed on the webpage.

17 Certainly we also have the  
18 definitions of the study progress if the  
19 protocol is pending or overdue or study is  
20 pending or on time. Those definitions are not  
21 in the guidance document but they are also in  
22 our publicly available website. Whoever is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 interested to look for the status, they can  
2 certainly link to those definitions and as  
3 they go through the webpage document.

4 In addition to our internal  
5 tracking system the CDRH has also launched the  
6 publicly available website, as I said. We did  
7 that earlier this year with an overall goal to  
8 increase the transparency of the Post-Approval  
9 Studies Program.

10 What we do post is really very  
11 general information but consistent information  
12 on all post-approval studies that were  
13 initiated since 2005 when we took the lead  
14 responsibility for their review. This is how  
15 that website looks like.

16 As you can see, we have several  
17 columns there. We have application number.  
18 We can also have applicant name. We have  
19 device name. We also have the medical  
20 specialty and the date when PMA was approved.

21 We also have straight from the approval order  
22 the brief description of the post-approval

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 study that was imposed by the PMA order. Then  
2 we also have the time when the protocol  
3 approved and then the status.

4 Certainly this webpage is linked to  
5 the PMA database and the person who is looking  
6 into this can quickly link to that and get the  
7 basic information on this PMA. Certainly we  
8 have links to the guidance document and  
9 frequently ask questions. We feel it is  
10 pretty friendly and easy to navigate the  
11 website.

12 Another important initiative that  
13 had just started this year is the Post-Market  
14 Advisory Panel Update. We certainly, as I  
15 said, view panel input as critical to us  
16 assessing the safety and effectiveness of  
17 medical devices. We felt that in the past we  
18 didn't really do a good job in giving you  
19 feedback on how the study that you recommended  
20 during deliberations really are progressing.

21 We felt that there are two types of  
22 updates that we would like to give you. We

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 started doing the general post-approval study  
2 updates in November of this year so this is  
3 the second one. We anticipate that at every  
4 panel meeting we will be able to provide that  
5 to the panel members.

6 Also for certain portion of the  
7 post- approval studies we do want to bring  
8 more in- depth updates to the panel and you  
9 will hear one today, this morning, on the  
10 ExAblate device. We have presented one to the  
11 Neurological Devices Panel in January and,  
12 again, this is the second one that we are  
13 bringing to you.

14 The part of this process is really  
15 we stick with the sponsor. We obtained an  
16 agreement that the sponsor would like also to  
17 come and present and we will share this  
18 presentation. First the sponsor will present  
19 and then the FDA. Hopefully this will bring  
20 some useful information to the panel.

21 We certainly believe that the  
22 success of the Post-Approval Studies Program

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is highly dependent upon effective partnership  
2 between the FDA, industry, and other  
3 stakeholders. In that spirit we had organized  
4 and co-sponsored the first conference with the  
5 goal really to hear and listen to the  
6 stakeholders on the status of those efforts.

7 We plan to continue dialogue with  
8 stakeholders and some of them include ARC,  
9 NIH, CMS, certainly medical devices  
10 associations, contract research organizations,  
11 IRBs. We will invite panel members as well to  
12 hear how we can best proceed in improving the  
13 program.

14 Now, let's just move on quickly.  
15 Again, this was meant just because it's a  
16 public session just to give an overview of the  
17 studies that we currently have ongoing in the  
18 OB-GYN arena. You can see there are only  
19 three ongoing studies that were initiated in  
20 2005.

21 These studies, all three, are  
22 observational studies, one-arm studies, one

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 for tubal occlusion device or the permanent  
2 birth control, another one thermal balloon  
3 endometrial ablation system, and the third one  
4 optical detection system for cervical cancer.

5           Again, the goal that we have to  
6 increase the scientific rigor of the  
7 post-approval study is something that cannot  
8 be reached overnight. We are looking  
9 specifically to panel support and guidance to  
10 make sure that our studies in the future are  
11 designed with higher scientific rigor. We  
12 heard yesterday a lot of discussions about the  
13 need for control group and clear objectives.

14           Again, you have to understand that  
15 some of our current thinking really is driven  
16 by the existing practice and a change cannot  
17 occur overnight in case you had some questions  
18 about the study design of these studies.

19           As I said, the goal is to have  
20 agreed upon post-approval study protocols at  
21 the time of the PMA approval. That goal is  
22 achieved in two out of three protocols for the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 OB-GYN devices.

2 Two are agreed at the time of the  
3 approval and one outline was agreed at the  
4 time of the approval but then full protocol  
5 was agreed upon within three months after the  
6 approval order. The goal is really to reduce  
7 the gap between the approval order and the  
8 initiation of the post-approval study.

9 As far as how those studies are  
10 progressing, one report is overdue received  
11 which means it came a little bit after the due  
12 date but it was still received and we marked  
13 it as such on the webpage. Two of the PMAs  
14 were approved in 2007 and the first reports  
15 are not due yet.

16 One of them is due December 14th,  
17 actually today, and the other one is January  
18 8th. We will review them as soon as they  
19 come. We usually give ourselves -- we make a  
20 commitment that we will review them within 60  
21 days.

22 This is how the studies are

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 progressing. One study is on hold. You have  
2 heard that during the course of the session  
3 this morning. The other two studies are  
4 pending initiation and these are the dates  
5 when the protocol was approved and they are  
6 still pending.

7 This is just the last slide, really  
8 what is our vision. We would like the studies  
9 to answer important post-market questions. We  
10 also are committed that the studies we design  
11 are going to be based and founded on good  
12 science.

13 We certainly strive for those  
14 studies to be timely accurate and provide you  
15 results. We also have a goal that we receive  
16 the reports clearly identified and effectively  
17 track. I cannot stress enough how important  
18 for us it is to keep our stakeholders apprised  
19 including the panel members.

20 Not only that but our collaboration  
21 within the center is such an essence of the  
22 program that we rely very heavily on our

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 pre-market colleagues for the technical  
2 expertise and their historical knowledge of  
3 the post- approval studies as they were  
4 happening before we took over.

5 We believe with this proactive  
6 approach we will see less enforcement actions.

7 We will use them as needed but we believe  
8 that if we do the studies for the first time  
9 right, it's going to be less need for  
10 enforcement option.

11 This is just how the Epidemiology  
12 Branch looks like. We have 19  
13 epidemiologists. In blue you have the ones  
14 that are involved in review of post-approval  
15 studies for OB-GYN devices. Also we have  
16 project managers that help us move those  
17 reports forward and are in constant touch with  
18 the sponsors.

19 I would also like to introduce the  
20 Cardiovascular Devices team leader, Dr. Loyo-  
21 Berrios and she is actually going to be the  
22 one presenting the update on the ExAblate

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 study design.

2 We believe that by setting these  
3 goals and all the changes that have happened  
4 in the last two years, we really raised the  
5 bar and those represent a higher expectation.

6 Heightened expectations, however, often bring  
7 heightened concerns about burden, workload,  
8 perceived fairness, and added value. It is up  
9 to us and our stakeholders to discuss it  
10 openly, responsibly, and collaboratively.

11 We understand the concerns but we  
12 also have to put them into a larger context of  
13 asking and answering the right post-market  
14 questions. We welcome an exchange of ideas on  
15 diverse methodologies that may be cost  
16 effective, innovative, and productive. We  
17 value all approaches and data sources that  
18 will give us high quality answers to the right  
19 post-market questions.

20 With that, I would like to conclude  
21 my presentation. Again, if you have any other  
22 suggestions or ideas how to improve the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 program, this is my contact information and I  
2 would be happy to listen to those and  
3 incorporate them into our procedures. Thank  
4 you.

5 CHAIR CEDARS: Thank you very much  
6 for that presentation.

7 We will now move on to the next  
8 topic on our agenda, Post-Approval study  
9 update on the ExAblate 2000 System from  
10 InSightec, Inc. Prior to the hearing  
11 presentations from the FDA and InSightec we  
12 will hold a 15-minute open public hearing for  
13 this meeting. I just want to remind people  
14 that the open hearing portion for this morning  
15 is solely on the ExAblate system.

16 Is there anyone in the audience who  
17 would like to address the panel? If so, if  
18 you could please raise your hand. If not,  
19 then we will move on into the more formal  
20 presentations. We will now hear from  
21 InSightec regarding post-approval study for  
22 their ExAblate 2000 system.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 CHAIR CEDER: Dr. Peterson?

2 DR. PETERSON: While we're waiting,  
3 I just wanted to say congratulations and  
4 thanks to the branch and the division and the  
5 center for the work that you're doing with the  
6 post- market surveillance program. I just  
7 think it's tremendous and hugely contributing  
8 to the mission in general. Just  
9 congratulations.

10 Just speaking for myself, the vote  
11 yesterday for premarket approval was because  
12 of a belief that the post-market process would  
13 address the concerns that I have. So thanks.

14 DR. ALIKACEM: Good morning. I'm  
15 going to thank the panel for their time, and  
16 also to thank the FDA agents or representative  
17 for presenting us with this opportunity to  
18 present our results and put the results into a  
19 certain perspective.

20 As a manufacturer, I would like to  
21 add one more comment. Other than some  
22 confusion at the beginning of the post-PMA

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 surveyance, we have pretty much enjoyed  
2 interacting with the FDA and submitting our  
3 reports on time as requested by the FDA. This  
4 has somewhat surprising seamless burden on us  
5 other than some financial costs that is  
6 associated with the regular reporting.

7 First of all, I'm Nadir Alikacem,  
8 I'm the Pole Manager for the InSightec  
9 representing the company in North American  
10 activities.

11 My presentation is centered around  
12 three or four key points. I would like first  
13 to start with a brief description with the  
14 device just to remind the audience of what the  
15 ExAblate system is all about. Then I would  
16 move on to the post-PMA requirements by  
17 describing the study cohorts and treatment  
18 guidelines, and some results.

19 The ExAblate system is based on the  
20 principle of thermal ablation. The thermal  
21 ablation is when you a heat a tissue to  
22 certain temperature, you can achieve 100

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 percent tissue necrosis. This tissue  
2 reaction to temperature is not linear. The  
3 plot that's presented here is very good  
4 presentation of how this reaction of the  
5 tissue to the temperature and time  
6 combination. The ExAblate algorithm of the  
7 ablation is based on this concept.

8 The technology of the ExAblate  
9 system is based on -- I'm just trying to --  
10 these are small, the animation, I'm trying to  
11 switch to the other settings. I apologize  
12 about this.

13 The ExAblate technology, which is  
14 basically focused ultrasound has been around--  
15 I mean the focused ultrasound technology has  
16 been around for quite awhile. What is really  
17 novel about the ExAblate is its marriage with  
18 the MR technology. Indeed, the ExAblate  
19 system is fully integrated to an MRI system,  
20 specifically GE based MR scanners. And why is  
21 this?

22 The main point that suffered from

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the old technologies that there is really no  
2 feedback or guidance on how to provide  
3 treatment planning of the focused ultrasound  
4 ablation of targeted tissue. The MR component  
5 provide three dimensional planning  
6 capabilities as well as tailoring the  
7 treatment according to the safety and the  
8 anatomy description and geometry. It provides  
9 also real time telemetry. This is really key  
10 component to allow to determine the level of  
11 ablation achieved on the fly during the  
12 treatment itself.

13 And most of all, finally, the  
14 post-treatment evaluation. This is done while  
15 the patient is still on the table while the  
16 patient is still in position you can evaluate  
17 the effect of the treatment on treatment day  
18 immediately after the treatment is completed.

19 So basically this is the device  
20 that the ExAblate is all about.

21 As I said earlier, the ExAblate  
22 system was approved by the FDA in 2004. As

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 part of the approval order there was some  
2 conditions, and among other things is to have  
3 some postmarket studies and follow ups.

4 Basically we are responsible to  
5 report on three major groups. Groups A being  
6 the original set of patients that were part of  
7 the pivotal study. The number of these  
8 patients at treatment day was 109 patients.

9 Just for refreshment a little bit,  
10 this study had a control arm. The control arm  
11 was total hysterectomy, abdominal  
12 hysterectomy.

13 Then we had 160 patients part of  
14 the continued access.

15 And finally, post-approval we were  
16 asked to do a study targeting specifically  
17 effecting American patients limited  
18 exclusively to the African-American patients.  
19 Due to sort of the prevalence of uterine  
20 fibroids in this particular patient population  
21 and the symptomatology that comes with it.  
22 And during the original pivotal study that was

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1       judged by the panel that there was not enough  
2       for presentation from this particular patient  
3       population, so we were mandated to perform the  
4       study according to the labeling treatment  
5       guidelines.

6                       These three patient cohorts  
7       basically were treated under different  
8       guidelines. And this is really the key  
9       element in how these treatment guidelines are  
10      impacting the post- PMA surveyance and data  
11      collection and follow up.

12                      Because unless we understand the  
13      impact of these treatment guidelines on the  
14      outcome of the treatment, it's very difficult  
15      to evaluate these long term follow ups and  
16      make sense of them. Let me first start with  
17      the first group of patients.

18                      These are the original treatment  
19      guidelines. I won't read them to you  
20      one-by-one, but as you can see just from the  
21      diagram when you combine all these treatment  
22      guidelines, you can see that the treatment

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 area that is basically allowed by these  
2 clinical protocol becomes very restrictive.

3 Is there a way to change the field  
4 of view of this presentation? Because there's  
5 some data that's contained on the bottom.

6 Anyway, the data that I'm showing  
7 on the bottom there will be duplicated in a  
8 couple of slides. But what I'm showing here  
9 basically is that the net effect of these  
10 treatment guidelines led to a 25 percent -- a  
11 mean of 25 percent perfused volume. This is  
12 for the pivotal study here and this is for the  
13 group B1.

14 The group B1 of patients during the  
15 continued access in negotiation and discussion  
16 with the FDA representative, at the second  
17 time during the continued access study  
18 treatment guidelines were changing almost in  
19 real time. So there has been several changes  
20 along the way.

21 So the group B1 is the set of  
22 patients that were treated under the original

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 guidelines. And the mean non-perfused volume,  
2 which is the net effect of the treatment, was  
3 approximately 20 percent. So this particular  
4 set of patients had a net effect treatment of  
5 no more than 25 percent at baseline.

6 Then like just as I said a minute  
7 ago, the second group of these continued  
8 access cohort patients were treated under  
9 different guidelines, somewhat restrictive but  
10 literally speaking compared to the first  
11 group, a little bit more enhanced guidelines.  
12 The net effect of these guidelines, again, was  
13 approximately 29 percent at baseline.

14 Finally, the group of  
15 African-American patients that was done under  
16 the sort of labeling treatment guidelines and  
17 during part of the post-PMA requirement, the  
18 net effect of these treatment guidelines was  
19 approximately 37 percent.

20 One very important key element in  
21 here is that this 1.5 cm to serosa. If you  
22 take a fibroid of approximately 6 cm in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 diameter, this 1.5 cm represents 58 percent of  
2 the volume. So just there we are not going to  
3 be able to achieve the 50 percent of ablation  
4 that is allowed per labeling. And depending on  
5 the size of the fibroid, that can increase or  
6 decrease.

7 So one of the sort of interesting  
8 outcome of all of this is that now in the  
9 post-PMA follow up we can very easily say that  
10 these treatment guidelines are no more than  
11 less than a thermal dose escalation of the  
12 ablation of the fibroid with the ExAblate  
13 system. So what we are following in long term  
14 fashion is the analyses of these dose  
15 escalation and durability of the ExAblate  
16 system. And that's what we've been reporting.

17 Let me first start with the safety  
18 profile. This is the safety profile from the  
19 premarket cohort. And this is just to refresh  
20 the memory of some of the panel members who  
21 are present here who were present at that  
22 time.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           The safety profile, the preliminary  
2 I should say, the safety profile of the  
3 African- American patients that were treated  
4 in a post- PMA under the somewhat increased  
5 treatment guidelines shows no new adverse  
6 events that haven't been identified previously  
7 or that the safety profile has changed  
8 considerably from what was established  
9 previously.

10           One of the key elements to report  
11 off of this post-PMA is the symptom severity's  
12 course over time for each group of these  
13 patients. We presented the data here for two  
14 reasons.

15           One is to show the produceability  
16 of these data post ExAblate treatment. This  
17 is the data in yellow of the original set of  
18 patients and those that are in blue are the  
19 data from the -- collected from to date as of  
20 June 2007 from the African-American study.

21           Just as expected if you look at the  
22 mean symptoms or at the baseline, the African-

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 American study shows a slightly higher  
2 symptomatology compared to the other groups.

3 This is really the key element in  
4 all of our studies that we are finding out in  
5 this post- PMA long term follow ups: Is that  
6 if you look at the net effect of the treatment  
7 guidelines for group A, B1, B2 and C you'll  
8 see that the mean baseline in non-perfused  
9 basically gradually increased and that is  
10 reflected in the percent distribution of  
11 alternative treatments for each of the groups.

12 This group here is the original  
13 pivotal study where the bar in green is the 36  
14 months. This group have completed their  
15 studies.

16 And then this is the group B one.  
17 So you can see the effect of 25 percent non-  
18 perfused of the baseline led to approximately  
19 48 percent alternative treatments at 36. This  
20 is not surprising if only of a quarter of the  
21 fibroid that is treatment, one should not be  
22 surprised of a long-term durability of the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 treatment. However, by comparison if I took  
2 the African- American study outcome and the  
3 non-perfused volume at baseline, the mean I  
4 should say, the impact is quite different.  
5 You can see it from there.

6 The study is still ongoing, so the  
7 data is still preliminary. But you can see at  
8 24 months the preliminary data showed that  
9 there is a significant difference between the  
10 two groups or the three groups of patients.  
11 This is really a very important key point that  
12 we would like to stress as the FDA  
13 representative will go into more details,  
14 presentation of this data.

15 Bear in mind that, I'm sure you  
16 know this much more than I do, that this group  
17 of African-American patients due to the  
18 prevalence of the fibroid symptomatology and  
19 so on are really sort of the most symptomatic  
20 fibroids that one can encounter if one divides  
21 the population in subgroups.

22 Another element that we were

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 required to capture part of this post-PMA  
2 surveyance and reporting is pregnancies. Even  
3 though the ExAblate was cleared for the  
4 inter-IDE approvals and under PMA approvals  
5 for patients that are family complete, we were  
6 asked to monitor any patient that becomes  
7 pregnant and to report that data. Under this  
8 requirement and for this three groups we have  
9 captured four patients who were pregnant from  
10 all of these cohorts of patients. All of them  
11 carried into the third trimester. Three of  
12 them had the vaginal deliveries and one of  
13 them had c- section. This particular patient  
14 had prior history of C-sections.

15 The average weight of the babies  
16 was approximately 3300/3400 gr. And one  
17 postpartum complication for the baby that had  
18 a collapsed lung and was sent to ICU for a  
19 couple of days.

20 Obviously, worldwide, we have a  
21 larger number of patients pregnant and with  
22 more data.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           In summary, as a company we believe  
2           that the preliminary data suggests that the  
3           overall safety profile of the ExAblate for the  
4           application of the uterine fibroid is quite  
5           acceptable. And there has been no significant  
6           relation through thermal dose escalation  
7           regimes in terms of effecting the safety  
8           profile of the device.

9           From an efficacy perspective,  
10          obviously the major sort of outcome of these  
11          dose escalation regimes is the net  
12          effectiveness is really dependent on the  
13          amount of treatment that a patient may get on  
14          the day of treatment. The three guidelines  
15          that these patients were treated under were  
16          pretty restrictive, and therefore the data  
17          truly represents the effect of these  
18          restrictions on the final outcome.

19                   Thank you.

20           CHAIR CEDER: Thank you. And I'd  
21          like to hold questions until after the FDA has  
22          given their presentation.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1                   We'll now hear the FDA's  
2 presentation regarding post approval studies  
3 for the InSightec ExAblate 2000 system. And  
4 this will be presented by

5                   DR. BAILEY: This presentation will  
6 be given by Dr. Nilsa Loyo-Berrios.

7                   DR. LOYO-BERRIOS: Good morning,  
8 members of the panel and of the audience.

9                   My name is Nilsa Loyo-Berrios. I'm  
10 a team leader in the Epidemiology Branch of  
11 the Division for Post-Market Surveillance in  
12 the Office of Surveillance and Biometrics.

13                   Today I will present a  
14 post-approval study of data for the ExAblate  
15 2000 system.

16                   I will start by presenting a short  
17 description of the device and will continue  
18 with pre-market and will describe the approval  
19 commitments. I will also present a  
20 description of the study cohorts' preliminary  
21 results. And I will conclude with discussion  
22 and closing remarks.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           The InSightec ExAblate 2000 system  
2           is a noninvasive thermal ablation device that  
3           it's fully integrated with the MR imagining  
4           system. And it is used for ablation for  
5           uterine fibroids.

6           There are three components. The  
7           operator, console, the patient table, the  
8           equipment cabinet that includes the interface  
9           electronics of the patient table, the MR  
10          scanner and the operator console.

11          The device is indicated for use in  
12          perimenopausal women with symptomatic uterine  
13          fibroids who desire a uterine sparing  
14          procedure. And it is contraindicated for use  
15          in women who should not undergo magnetic  
16          resonance imagining and if the clinician is  
17          unable to avoid having important structures in  
18          the path of the ultrasounding.

19          And I shall also mention that  
20          patients should have completed childbearing.

21          This PMA was filed in January of  
22          2004 and it was granted expedited review

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 status. And it was approved in October of 2004  
2 with conditions of approval.

3 Post-approval commitments included:

4 To continue follow up of the  
5 premarket cohorts for 3 years. And this was to  
6 collect long-term safety and effectiveness  
7 data. And the data included symptom severity,  
8 fibroid re-grow, use of alternative  
9 procedures, pregnancies and serious adverse  
10 events.

11 The premarket cohorts  
12 African-American women were under represented.  
13 There was 11 percent in the pivotal study and  
14 10 percent in the continued access study. And  
15 because African- American tend to have a  
16 higher prevalence of uterine fibroids, the FDA  
17 considered it was necessary to conduct a  
18 post-approval study to evaluate device  
19 performance in this group.

20 Therefore, the second post-approval  
21 commitment consists of enrollment of a new  
22 cohort of African-American woman to evaluate

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the postmarket short and long-term safety and  
2 effectiveness.

3 Similar symptom and fibroid data  
4 has been collected for this cohort. And in  
5 addition we're also collecting history of  
6 c-section for this group.

7 The premarket studies, that is the  
8 pivotal study and the continued access study,  
9 were originally designed for a 6 month follow  
10 up period and then later extended to include  
11 12, 24 and 36 month follow up visits.

12 The post-approval study cohort is  
13 designed to include follow up through the 36  
14 month after treatment.

15 The data included in this  
16 presentation is based on the latest  
17 post-approval study report that was received  
18 at the FDA at June of 2007. This table  
19 presents data on the follow up studies for  
20 each study cohort.

21 Enrollment is completed for the  
22 three cohorts and the pivotal study has

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 completed follow up of the study subjects.

2 The continued access study and the  
3 new cohort are still ongoing. And for far  
4 long- term data as defined at 36 months  
5 assessment is available for 57 patients out of  
6 342.

7 In the next couple of slides I will  
8 describe in detail the patient accountability  
9 for each cohort separately.

10 For the pivotal cohort most of the  
11 study dropouts are related to alternative  
12 treatment or second ExAblate treatment. Women  
13 that need additional treatments are followed  
14 to that point. And when they have the second  
15 treatment, they are excluded from follow up.  
16 And for this cohort this represents about 48  
17 percent of them.

18 About 26 percent were lost to  
19 follow up, but this is due to reconsenting the  
20 patients for a longer follow up than  
21 originally planned. And as I mentioned in my  
22 previous slide, this cohort has already

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 finished follow up and long term data, that is  
2 the 36 assessment, is available for about 27  
3 percent of them.

4 For the continued access cohort,  
5 again most of the follow exclusions are  
6 related to having additional treatment. And  
7 for this cohort that's about 43 percent.  
8 Follow up is still ongoing and so far data 36  
9 month assessment is available for about 18  
10 percent.

11 There were four pregnancies in this  
12 group and they were excluded from follow up.  
13 And I'll present more details about the  
14 pregnancies later in the presentation.

15 For the new post-approval cohort  
16 most of the follow up exclusions are related  
17 to those that have been lost to follow up, and  
18 this includes women that declined  
19 participation, those who volunteered refuse,  
20 and those who the sponsor was not able to  
21 contact. About 14 percent needed alternative  
22 treatments or second ExAblate treatment, and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 71 percent of this cohort is still being  
2 followed. And none of them have reached the 36  
3 month assessment yet.

4 So therefore, in terms of overall  
5 patient accountability, and this table is made  
6 just to present the number of patients for  
7 which we have data. The initial total sample  
8 size was 342 for which data on the 36 month  
9 assessment is available for 17 percent.

10 About 37 percent needed alternative  
11 or second treatments and they were excluded  
12 from the follow up. And 28 percent is still  
13 being followed.

14 As you heard from the sponsor, each  
15 study cohort was treated under different  
16 treatment guidelines. And because of these  
17 differences, the results, the study results on  
18 safety and effectiveness cannot be combined.

19 So this table shows the guidelines  
20 used for each cohort. And the main difference  
21 is related to the amount of fibroid, the  
22 volume that was allowed to be treated, the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 time for treatment duration and the  
2 availability of having a second treatment  
3 within the first two weeks.

4 So just to be more specific, the  
5 limited guidelines allowed for 50 percent of  
6 the fibroid volume to be treatment -- I mean,  
7 sorry, for 30 percent of the fibroid to be  
8 treated versus the extended guidelines that  
9 allow for 50 percent.

10 The limited allowed for 120 minute  
11 treatment time versus the 180 minutes allowed  
12 in the extended guidelines.

13 And the extended guidelines allow  
14 for the second treatment within the two weeks  
15 after the first treatment, which the limited  
16 guidelines did not allow.

17 Then the pivotal cohort was treated  
18 under the limited guidelines. The first 96  
19 patients of the continued access study, and  
20 those are labeled at a group B1, were treated  
21 under limited guidelines. The rest of the  
22 patients from the continued access studies,

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 those are group B2, were treated under  
2 extended guidelines. And the new post-approval  
3 cohort has been treated under labeled  
4 guidelines or what we call commercial  
5 guidelines, which are very similar to the  
6 extended guidelines.

7 So as I mentioned earlier in the  
8 presentation, since there are two cohorts that  
9 are still under follow up, the data results  
10 presented here represent preliminary results.  
11 These chart represents the effectiveness  
12 results based on the mean scores observed in  
13 the symptom severity subscale of the quality  
14 of life questionnaire. This is self-reported  
15 and it is considered a qualitative measure.  
16 But in general, smaller scores represent  
17 better quality of life.

18 And as you see, for each treatment  
19 group preliminary data show that the main  
20 effects are within the first six months after  
21 treatment, and it seems to be sustained over  
22 time. But please remember that the women that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 needed additional treatments are excluded from  
2 follow up at the time they have the second  
3 treatment. So, therefore, the results only  
4 represent women on -- the first ExAblate  
5 treatment was successful.

6 And also when we need to keep in  
7 mind that the comparability of the three  
8 groups is limited due to the differences in  
9 treatment guidelines and the raise  
10 distribution.

11 The continued access study and the  
12 pivotal study were mostly white, whereas the  
13 new cohort is composed of African-American.

14 This chart represents the incidents  
15 rates per 100 person months for a ten point  
16 improvement in the symptom severity score. And  
17 for each study group, the incident rates  
18 starts decreasing after six months post  
19 treatment. And if we look at any improvement  
20 in the scores, similar results are observed.

21 This chart represents the  
22 preliminary results for fibroid regrowth and

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the data shows that the fibroid volume  
2 decreases over time and it remains the  
3 baseline values. For the African-American  
4 cohort, there seems to be a slight increase  
5 after the six months. But since most of this  
6 cohort is still being followed, this trend may  
7 change once more patients complete follow up.

8 So moving on to safety, before the  
9 safety data is presented we need to know that  
10 the data does not include the study -- and  
11 their safety profile may be different, could  
12 be different.

13 The latest possible study report  
14 shows that since product approval there have  
15 been no adverse events to report in the  
16 pivotal or the continued access study. In the  
17 new postmarket cohort there have been no  
18 device related deaths, life threatening  
19 injuries or permanent injuries, acute  
20 hospitalizations or device related emergency  
21 interventional procedures. However, there have  
22 been known significant anticipated adverse

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 events, and that's what I'm presenting in this  
2 table.

3 The most common event were related  
4 to pain and discomfort with 1.9 per 100  
5 patient months incidence, followed by urinary  
6 adverse events with that 1.3 per 100 person  
7 month incidence.

8 And the overall incidence for  
9 nonsignificant anticipated adverse events,  
10 it's 5 per 100 per 100 months incidence.

11 Most of the adverse events were  
12 mild and were resolved in less than two weeks.  
13 And four events of pain related to some  
14 medication were reported as severe. All four  
15 resolved the same day without interventional  
16 therapy.

17 And this chart represents the  
18 cumulative incidence rates for 100 person  
19 months for the need for additional treatment.  
20 And the preliminary results show that the rate  
21 seems to increase within the first six months  
22 after ExAblate treatment, and then it looks

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 like it decreases over time. And what  
2 happened after the 36 months, we don't know  
3 because we don't have any more data beyond  
4 that.

5 And, again, the continued access  
6 and the African-American group are still being  
7 followed.

8 So before I talk about pregnancy  
9 data, I would like to remind you that the  
10 device is not intended for use in women who  
11 are seeking to become pregnant. So the  
12 observed pregnancies could have happened in  
13 women who became pregnant inadvertently, that  
14 means that was not planned, or who became  
15 pregnant against medical advice.

16 I would also like to remind you  
17 that these studies are designed to evaluate  
18 the association between the device used and  
19 the occurrence of pregnancies, or pregnancy  
20 related complications. So these data are  
21 really descriptive of what has been observed  
22 in the post-approval studies.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           There are four women, as I  
2 mentioned earlier, in the continued access  
3 study who became pregnant. There is only one  
4 complication to report. The mother needed a c-  
5 section because she had a history of c-  
6 sections. And her baby spent several days in  
7 the neonatal intensive care unit due to a  
8 collapsed lung. The birth weight of the baby  
9 was 3425 grams. And the APGAR scores were  
10 reported as 8/8.

11           No other complications are reported  
12 for the other pregnancies. And the average  
13 birth weight for all the pregnancies is 3398  
14 grams.

15           And currently so far no pregnancies  
16 have been reported in the pivotal or the new  
17 post- approval study cohort.

18           So this table represents the data  
19 on the c- section history that has been  
20 collected for the new post-approval study.

21           There are ten women in this new  
22 cohort with history of c-section, and six of

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1       them had experience adverse events.

2                       Two of the events were of mild  
3 severity, that's the abdominal pain and  
4 tremor, and one was moderate and three were  
5 classified as severe. And two of which  
6 happened in the same patient.

7                       So, again, these are -- since there  
8 are two studies are still ongoing, the data  
9 represent preliminary results. But so far for  
10 each study cohort there seems to be an effect  
11 within the first six months post-treatment  
12 that looks like it is sustained over time.  
13 And this is understanding the limitation that  
14 it only represents the women in whom the  
15 ExAblate treatment, the first treatment was  
16 successful.

17                       As mentioned earlier, about 48  
18 percent of the pivotal cohort, 41 percent of  
19 the continued access and 14 percent of the new  
20 cohort needed additional treatments.

21                       The need for additional treatments  
22 increases within the first six months

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 post-treatment, and then it stabilizes over  
2 time.

3 The rate so far is lower for the  
4 postmarket cohort and this it is important to  
5 know that although the results may not be  
6 generalizable to other race group, this cohort  
7 provides very valued results for the  
8 African-American women who we know have a  
9 higher prevalence of uterine fibroids.

10 The cohort is still ongoing,  
11 therefore final results are needed before any  
12 conclusions can be paid.

13 In terms of safety, the data shows  
14 acceptable with market safety profile. But,  
15 again, we need to know that the data does not  
16 represent the experience of the study  
17 dropouts, and their experience could be  
18 different.

19 So ExAblate is a non-invasive  
20 option for the treatment of uterine fibroids.

21 The extended follow up of the premarket  
22 cohorts provide a good estimate for the need

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of additional treatment for the women that  
2 were treated under limited guidelines. And the  
3 follow up of the new postmarket cohort  
4 provides the opportunity to evaluate if the  
5 need for additional treatments is decreased,  
6 but again understanding the limitation that it  
7 provides valued results for African-American  
8 women known to have high prevalence of uterine  
9 fibroids. That these are preliminary study  
10 results and the results may not be  
11 generalizable to other race groups.

12 And I would like to conclude my  
13 presentation acknowledging the people from the  
14 review teams from the premarket and postmarket  
15 programs in the FDA.

16 And now the floor is open for  
17 questions.

18 CHAIR CEDER: Thank you.

19 At this time I'd like to open the  
20 panel or the session for questions from the  
21 panel. And please do remember that these  
22 questions deal primarily or really solely with

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the postmarket studies.

2 DR. STUBBLEFIELD: I'm wondering  
3 why you chose not to continue following women  
4 that needed to be retreated? It seems like  
5 that would be an opportunity to continue to  
6 learn.

7 CHAIR CEDER: And we have perhaps  
8 the FDA and then the company answer that as  
9 well.

10 DR. LOYO-BERRIOS: I was not  
11 involved when they were designing the study.  
12 But I do understand why the women are  
13 excluded. And that is because once they have a  
14 second treatment, then the data doesn't  
15 represent the effectiveness of the device of  
16 the first treatment.

17 CHAIR CEDER: Can the sponsor  
18 address that question as well, please?

19 DR. ALIKACEM: There are two main  
20 points that can be derived from this  
21 particular question. The first one, the idea  
22 that these patients who went to alternative

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 treatment did not have a safety profile at the  
2 exit from the actual study is not correct.  
3 Other than lost to follow up where patients  
4 did not communicate their experience, all the  
5 patients that were exited due to alternative  
6 treatment provided their safety profile at the  
7 time of the exit from the study.

8 Patients who went to alternative  
9 treatments such as hysterectomy as an example,  
10 those patients are no longer representative of  
11 the device treatment, and not only from a  
12 safety perspective, but also obviously from an  
13 effectiveness perspective.

14 DR. STUBBLEFIELD: But those that  
15 were retreated --

16 CHAIR CEDER: Could you please come  
17 a little bit closer to the mic?

18 DR. STUBBLEFIELD: Those that were  
19 retreated

20 DR. ALIKACEM: With the ExAblate  
21 device?

22 DR. STUBBLEFIELD: Yes, with the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 ExAblate, you do have information?

2 DR. ALIKACEM: Well, the spirit of  
3 the protocol for the pivotal study did not  
4 allow that. Those were considered as treatment  
5 failures and therefore, were not followed. And  
6 that was also true for the -- let me say, for  
7 the first cohort patients under the continued  
8 access. Because the second treatment was not  
9 allowed and any patient going to alternative  
10 treatment being ExAblate treatment or not, are  
11 considered as treatment failures and they were  
12 counted as such.

13 Subsequent to approval of second  
14 treatment, those particular patients within --  
15 I should say second treatment within two weeks  
16 of the first, those patients are followed.  
17 They are part of the data that is presented  
18 here.

19 DR. STUBBLEFIELD: Yes.

20 DR. ALIKACEM: From effectiveness  
21 and safety.

22 CHAIR CEDER: I believe Dr. Sharp.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. SHARP: I just had a question  
2 about your follow up. I understand there are  
3 relatively few centers doing this, and it's  
4 probably hard to get them back to the centers.  
5 But what are you doing to try to follow up on  
6 the patients who were lost to follow up?

7 DR. ALIKACEM: This is very good  
8 question. Way back when we were doing under  
9 the IDE follow ups, we communicated to the FDA  
10 and we got the FDA nod that for each patient  
11 before our declared loss to follow up they  
12 need to be contacted at least three times. And  
13 then sent a certified letter after that before  
14 they are declared lost to follow up.

15 So there is an extensive effort to  
16 contact the patient by phone, by email or  
17 whatever the means and then by certified  
18 letter to the patient.

19 CHAIR CEDER: Dr. Zaino?

20 DR. ZAINO: I'm not sure if this  
21 question is entirely appropriate. So if it's  
22 not, please let me know. But it appears that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 in the postmarket cohort of African-American  
2 women that their mean volume is a little bit  
3 more than half of that of the original pivotal  
4 study cohort. And that their rates of serious  
5 or other adverse events is significantly less  
6 and the need for retreatment is significantly  
7 less. Has a test for trend been considered in  
8 terms of relationship between fibroid size and  
9 efficacy and adverse events?

10 CHAIR CEDER: Do you understand the  
11 question?

12 DR. ALIKACEM: Not really. No.  
13 That's what I was going to say.

14 DR. LOYO-BERRIOS: From the data  
15 that is presented in the progress reports it  
16 looks like it would be possible to do it, but  
17 at this time it's very early in the follow up  
18 process of this cohort. But that would be a  
19 really good idea to do.

20 CHAIR CEDER: Just for  
21 clarification for the sponsor, the question as  
22 I understand it was that the volumes were

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 smaller in the new recruits, the  
2 African-American population and they had a  
3 lower risk and a lower side effect and lower  
4 retreatment or alternative treatment. So the  
5 question was if there was a correlation  
6 between size of the fibroid and either side  
7 effects or need for alternative treatments,  
8 and that should be looked at.

9 DR. ALIKACEM: Let me clarify a  
10 point. Thank you for clarifying this point.

11 I'm not really sure whether these  
12 particular set of data you're referring to is  
13 coming from with respect to volume of fibroid.  
14 If I use my memory, the volume, the average  
15 volume of the third cohort is -- in fact, it's  
16 probably 10 to 20 percent larger than the  
17 pivotal study. So I'm not really sure whether  
18 that is the case. I apologize.

19 CHAIR CEDER: While Dr Zaino is  
20 looking at that, Dr. Hillard.

21 DR. HILLARD: So my questions  
22 relate to the patients who became pregnant

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 after the procedure. And so a couple of  
2 questions around that.

3 One, what efforts are made to  
4 inform women that this is intended to be a  
5 procedure for women who don't plan to have  
6 children in the future.

7 And the question of the FDA is what  
8 is the FDA's role in that? I'm looking at the  
9 website, and I see nothing about the  
10 indications being for women with no plans for  
11 future pregnancies.

12 DR. LOYO-BERRIOS: As far as I  
13 understand, the label and the indications for  
14 use should be clear that the device should not  
15 be used in women that are still looking to  
16 become pregnant. But beyond that, I don't  
17 think FDA has control of how the practice of  
18 medicine is done.

19 Do you have any other --

20 CHAIR CEDER: Is there any other  
21 comment from the FDA on this issue?

22 DR. ALIKACEM: I can tell you from

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 our perspective we emphasized this point  
2 extensively in all our clinical trials the  
3 rate of recruitment is very -- I mean just  
4 look at the age and that status of menopausal,  
5 you will see that in most instances if we can  
6 use age as a guide, in most instances most of  
7 the patients participating in the clinical  
8 trials declared their -- or counseled that  
9 this is truly for only those who have  
10 completed families or no desire to become  
11 pregnant in the future.

12 DR. HILLARD: If I were seeking  
13 information from the website, I wouldn't find  
14 that information.

15 DR. ALIKACEM: It's in the labeling  
16 of the device. I don't know about the FDA. I'm  
17 not talking --

18 CHAIR CEDER: Ms. Brogdon?

19 DR. MARINAC-DABIC: You are talking  
20 about the website, which one you referring to?

21 DR. HILLARD: The company,  
22 InSightec.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. MARINAC-DABIC: The company's.  
2 Okay.

3 DR. HILLARD: Yes.

4 CHAIR CEDER: Ms. Brogdon?

5 MS. BROGDON: We don't remember  
6 specifically where the information about where  
7 childbearing is complete, where that is  
8 exactly. Perhaps the firm could remind us  
9 where in the labeling, patient information  
10 booklet and training that appears?

11 DR. ALIKACEM: It's in the  
12 information for prescribers, I believe on page  
13 7.

14 MS. BROGDON: Would it also be in  
15 the patient information booklet?

16 DR. ALIKACEM: Correct. This is  
17 front and center everywhere in the clinical  
18 trial, in the information for prescribers and  
19 so on.

20 MS. BROGDON: So it's not a part of  
21 the indications for use, but it's elsewhere in  
22 labeling?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. ALIKACEM: Right.

2 MR. POLLARD: Maybe you could speak  
3 a little bit to the patient labeling and your  
4 training program? Because really the question  
5 is getting at how are women advised about this  
6 procedure with respect to childbearing being  
7 complete. And I'm pretty sure that there's  
8 professional labeling, there's patient  
9 labeling and there's training. So why don't  
10 you speak a little bit to that?

11 DR. ALIKACEM: First of all, I  
12 would like to differentiate or separate the  
13 two issues, the following two issues. That is  
14 what happens in the clinical trial which is  
15 100 percent responsibility of the sponsor.  
16 What happens in the physician. My hands are  
17 just as tied as the FDA hands. Because we  
18 cannot dictate medicine on physicians.

19 That said, we developed a training  
20 in collaboration with the FDA at the time of  
21 the device approval for to disseminate with  
22 the sale of the device. We have the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 information for prescribers, which is a quite  
2 extensive document that not only lists the  
3 contraindications that were derived from the  
4 pre-PMA study or from the pivotal study  
5 including the childbearing completion. And we  
6 have extensive technical training that lasts a  
7 couple of days to ensure the safe operation of  
8 the device.

9 And I should also say that we also  
10 from day one incorporated training on MDR  
11 reporting. This is one element that we felt  
12 it was our direct or indirect responsibility  
13 to enhance that mechanism and explain it to  
14 the physicians as we are training them for the  
15 device.

16 So there is also a patient  
17 information pamphlet that has been devised and  
18 developed with the FDA that is given to the  
19 physicians, including the information for  
20 prescribers during the training.

21 CHAIR CEDER: Ms. Brogdon?

22 MS. BROGDON: Yes. I'm told that

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the wording about for whom childbearing is  
2 complete is actually in the indications for  
3 use that we approved with this PMA. So that  
4 should be part of the advertising.

5 DR. ALIKACEM: Which it is. If  
6 it's not, I'll look into it. But it is.

7 CHAIR CEDER: So you may want to  
8 just confirm that that is on your advertising  
9 and website.

10 Dr. Zaino, do you want to just  
11 clarify?

12 DR. ZAINO: I'm not sure clarify,  
13 but at least to specify it looked on slide 17  
14 that you presented, and I may have  
15 misunderstood it, but it looked as if for the  
16 pivotal study it was about 335 cubic -- you  
17 show it as cubic centimeters. And the  
18 postmarketing cohort I think is in green and  
19 it looks like about 200. And maybe I'm  
20 mistaken. I couldn't find the data elsewhere  
21 in the presentation.

22 CHAIR CEDER: Yes. The color code

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 is different than the prior slide, which makes  
2 it confusing.

3 DR. LOYO-BERRIOS: These data comes  
4 from the latest report that was submitted on  
5 June of 2007 to the agency.

6 CHAIR CEDER: So it does look as  
7 though the new postmarket cohort has a small  
8 uterine volume or fibroid volume. So that  
9 should be looked at.

10 So at this time, I'd like to call  
11 this portion of the session to a close, and we  
12 will have a brief 15 minutes recess.

13 (Whereupon, at 10:41 a.m. a recess  
14 until 10:59 a.m.)

15 CHAIR CEDARS: I would like to ask  
16 people to take their seats, so we can begin  
17 the next portion of the session. I will now  
18 move on to the general topics discussion  
19 regarding endometrial ablation for cessation  
20 of menses. The FDA will now give their  
21 presentation regarding the general topic  
22 before the Panel today. Ms. Price?

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 MS. PRICE: Good morning, ladies  
2 and gentlemen and distinguished Members of the  
3 Panel. My name is Veronica Price. I'm a  
4 biomedical engineer and a reviewer in the  
5 Obstetrics and Gynecology Devices Branch. I  
6 would like to thank you for your attendance  
7 today and I look forward to an interesting  
8 discussion.

9 As most of you are aware, FDA has  
10 spent the last 10 years looking at non-  
11 resectoscopic endometrial ablation devices for  
12 treating women with menorrhagia. There has  
13 been some interest expressed in a new  
14 indication for endometrial ablation. This  
15 morning we will be discussing the use of  
16 endometrial ablation devices for women seeking  
17 elective cessation of menses.

18 I would like to remind the Panel  
19 that a pound package was prepared and set to  
20 you to prepare for today's discussion. The  
21 package contains some background information  
22 on this issue, a bibliography with published

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 articles related to today's discussion, which  
2 included the recent ACOG Practice Bulletin on  
3 endometrial ablation and draft discussion  
4 questions.

5 In my presentation this morning,  
6 I'll identify the purpose of the general topic  
7 discussion, provide some background on the use  
8 endometrial ablation in women with  
9 menorrhagia. I will identify the clinical  
10 study issues for elective use that we're  
11 seeking your input on.

12 I will then introduce my colleague,  
13 Dr. Xuefeng Li, to provide an overview of the  
14 use of objective performance criteria or OPCs  
15 in clinical trials. I will then return to  
16 discuss ethical considerations for this type  
17 of clinical study and then I will leave you  
18 with the discussion questions.

19 The purpose of today's meeting will  
20 be to obtain Panel input on the key clinical  
21 trial design issues for a new use of approved  
22 endometrial ablation devices, that is elective

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

(202) 234-4433

[www.nealrgross.com](http://www.nealrgross.com)

1 ablation of the endometrial lining of the  
2 uterus in premenopausal women and eliminating  
3 or perhaps reducing menstrual bleeding for  
4 women in whom childbearing is complete.

5 By way of background, I will remind  
6 everyone that to date, FDA has approved five  
7 endometrial ablation devices as indicated here  
8 in the slide. They were approved for the  
9 following indication: Ablation of the  
10 endometrial lining of the uterus in  
11 premenopausal women with menorrhagia due to  
12 benign causes for whom childbearing is  
13 complete.

14 As the Panel Members are aware, in  
15 evaluating PMAs for new medical devices, a  
16 determination of reasonable assurance of  
17 safety and effectiveness must be made in order  
18 for approval. In the case of the five  
19 endometrial ablation devices approved for use  
20 in women with menorrhagia, this determination  
21 was based on data obtained during multi-center  
22 randomized controlled studies.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           The safety analysis was based on  
2 the occurrence of adverse events observed in  
3 the clinical trial and were applicable adverse  
4 events from commercial use outside the U.S. I  
5 will discuss these events in more detail later  
6 in my presentation.

7           The primary effectiveness analysis  
8 was based on a measured reduction in uterine  
9 bleeding. I would like to spend a few minutes  
10 on this effectiveness measure, because it will  
11 be relevant to one of our discussion  
12 questions.

13           The Pictorial Blood Loss Assessment  
14 Chart or the PBLAC score was developed by  
15 Higham and validated by Janssen in the 1990s  
16 as a simple method for discriminating between  
17 menorrhagia and normal blood loss. It relies  
18 on a visual assessment of blood loss using a  
19 pictorial chart in which there is a series of  
20 diagrams representing light, moderate and  
21 heavily soiled pads and tampons.

22           After a study subject records all

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of her catamenial products used during her  
2 menstrual cycle on this chart a score is  
3 calculated using numerical values assigned to  
4 the various diagrams. The PBLAC has been used  
5 in pivotal studies to determine study  
6 inclusion, study subject success and  
7 amenorrhea.

8 All but one of the approved pivotal  
9 studies for endometrial ablation in women with  
10 menorrhagia required a score of greater than  
11 or equal to 150 for inclusion. There was one  
12 that required a score of greater than or equal  
13 to 185.

14 The definition for patient success,  
15 which was the primary endpoint for all  
16 approved studies required a score of less than  
17 or equal to 75 at 12 months post-procedure.  
18 Amenorrhea was the secondary study endpoint  
19 for these studies. It was defined as a score  
20 of zero at 12 months. We have a discussion  
21 question related to how PBLAC scores may be  
22 used in clinical studies for the proposed

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 elective use indication.

2 The table on this slide was  
3 included in your background package. I have  
4 included it here, because I think it will  
5 provide some useful background information for  
6 one of the discussion questions related to  
7 target success rate. This slide gives a quick  
8 summary of the amenorrhea rates achieved in  
9 women with menorrhagia using various  
10 endometrial ablation devices.

11 As indicated earlier, this was not  
12 the primary study endpoint. I think it is  
13 useful to note that there was a range in the  
14 amenorrhea rates from 14 percent to 55 percent  
15 in the experimental arm, which was the new  
16 device being tested. There was also a range  
17 of 25 percent to 47 percent in the control  
18 arm, which was the surgical control. The rate  
19 was relatively stable over the three year  
20 follow-up period, except in one case, but this  
21 was primarily due to a large loss to follow-  
22 up.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           With that background on where we  
2           have been with endometrial ablation, I would  
3           like to shift the focus to today's discussion  
4           topic and examine the clinical trial design  
5           issues for the new elective use indication.  
6           Some of the key clinical trial design issues  
7           that we will be asking for your input on today  
8           are listed here. There are the inclusion/  
9           exclusion criteria, outcome measures,  
10          including the primary endpoint and any  
11          secondary endpoints, the appropriate control  
12          group, if there is one, and the necessary  
13          follow-up.

14           As indicated in a previous slide,  
15          women with menorrhagia were defined as having  
16          a PBLAC score of greater than 150 for purposes  
17          of study entry. In this new population, we  
18          are interested in how we might define women  
19          with normal menstrual cycles. One option that  
20          we have considered is the use of a PBLAC score  
21          for study entry.

22           We would be interested in the

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 Panel's input on this option as well as other  
2 measures that may be used for study inclusion  
3 to capture this population. We are also  
4 interested in how we might ensure that women  
5 in the study have completed their  
6 childbearing. To that end, we are interested  
7 in the Panel's opinion on inclusion/exclusion  
8 criteria related to history of permanent  
9 sterilization and age or other factors. This  
10 is the topic of another discussion question.

11 With this new patient population  
12 and new definition of patient success needs to  
13 be developed, the most straightforward way of  
14 assessing success is the cessation of bleeding  
15 entirely or amenorrhea. Another option is a  
16 combined endpoint of amenorrhea and spotting.

17 If the primary outcome measure is  
18 to include spotting, then we would be  
19 interested in the Panel's input on the  
20 definition of spotting. That is no protection  
21 or use of a pantiliner and whether the  
22 definition should consider the predictability

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 of the spotting, whether it is cyclical or  
2 not.

3 We are also looking for the Panel's  
4 input regarding the time period at which  
5 success is determined. Again, for the  
6 menorrhagia patient, success was determined at  
7 12 months post-procedure. We believe that a  
8 secondary outcome measure related to quality  
9 of life is necessary for this study. We're  
10 interested in whether the Panel believes that  
11 patient satisfaction is sufficient or whether  
12 a more comprehensive questionnaire should be  
13 used. If so, what questionnaire might be used  
14 and whether it needs to be validated in this  
15 group of patients.

16 Study controls. The proposed use  
17 of endometrial ablation for elective use not  
18 only represents a new use for endometrial  
19 ablation devices for medical devices, there  
20 are no approved devices, but there also aren't  
21 any approved drugs for permanent cessation of  
22 menses in women with normal menstrual cycles.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1           As such, there is no clear control  
2 group for this type of study. Although there  
3 are oral contraceptives, which have an  
4 approved claim for extended menstrual  
5 suppression, the primary indication for these  
6 drugs is contraception and the menstrual  
7 suppression is reversible.

8           If the Panel agrees that there is  
9 no suitable control group, then we would be  
10 interested in how study success might be  
11 defined in a single arm study. We have  
12 examined two possibilities. One is to  
13 establish objective performance criteria and  
14 the other is to set a target success rate.

15           Although we do not believe that the  
16 use of an OPC in this instance is appropriate,  
17 we think it is useful to go through the  
18 exercise of describing what an OPC is and how  
19 we came to our conclusion. For this, I would  
20 like to introduce Dr. Xuefeng Li, a  
21 biostatistician, from our Office of  
22 Surveillance and Biometrics.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 DR. LI: Thanks, Veronica. Good  
2 morning, ladies and gentlemen, distinguished  
3 Panel Members and guests. My name is Xuefeng  
4 Li, a statistician in the Center for Devices  
5 and Radiological Health. I will give you a  
6 brief introduction of the objective  
7 performance criteria and discuss whether it  
8 can be used for endometrial ablation devices  
9 for the elective use.

10 Here the outline for my  
11 presentation. First, I will briefly introduce  
12 the definition of OPC. Then the advantages  
13 and disadvantages of OPC will be presented.  
14 After that, I will discuss how an OPC might be  
15 developed. And finally, I will briefly  
16 discuss the barriers yielding OPC for  
17 endometrial ablation devices with the new  
18 indication.

19 As the first step, let us establish  
20 an operational definition of the term  
21 objective performance criteria. The essence  
22 of OPC is that it is designed to be used as a

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 fixed target of value that shall be objective  
2 in a meaningful standard to provide a  
3 comparison by evaluating the safety and  
4 effectiveness of a medical device.

5 It is typically expressed at the  
6 rate, thus, the OPC is used as a surrogate for  
7 traditional control groups and the associated  
8 regular scientific and analytical methodology  
9 typically observed in medical device clinical  
10 trials. OPC serves as a benchmark of  
11 minimally acceptable value used in the past  
12 field approach in determining if a particular  
13 device or application is ultimately approved  
14 for marketing.

15 The potential advantages of OPC are  
16 the following: Generally, it requires a  
17 smaller sample size, provides a standardized  
18 comparison for all sponsors, saves  
19 considerable time and money and is  
20 logistically simpler to execute. In other  
21 words, if OPC is used appropriately, it may be  
22 less burdensome to conduct than traditional

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 medical device trials.

2           On the other hand, there are a lot  
3 of limitations associated with the use of an  
4 OPC. An OPC shares all the problems and risks  
5 associated with non-randomized control studies  
6 with historical controls. For example, the  
7 possibility of selection bias. Only limited  
8 historical data may be available for the  
9 development of an OPC.

10           Borrowing an OPC developed for  
11 different indication or patient population is  
12 problematic. An OPC obtained from literature  
13 review may be questionable, because, first, it  
14 may be subject to publication bias. Second,  
15 it is difficult to appropriately assess the  
16 pool-ability of patients across different  
17 historical studies without patient level data.

18           It is difficult to appropriately  
19 assess patient comparability between the  
20 current patient cohort and the historical  
21 patient cohort that was used to develop the  
22 OPC. In addition, it is not easy to determine

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 who should be responsible for developing an  
2 OPC for a particular device. Who should be  
3 responsible for checking if an OPC developed  
4 is appropriate and who should be responsible  
5 for updating an existing OPC?

6 Note that a trial with OPC is  
7 neither superiority nor non-inferiority  
8 comparison.

9 Here are more limitations. It is  
10 difficult to verify the validity of the  
11 historical data and conduct appropriate  
12 statistical analysis. OPC may be affected by  
13 advances in the practice of medicine. The  
14 sponsor, the FDA and the third party may be in  
15 disagreement on a final OPC value.

16 Sometimes it will be time and  
17 result intensive to develop an OPC. The data  
18 used to develop an OPC may become older and  
19 older, therefore, may no longer be relevant.

20 Now, let's see how an OPC should be  
21 developed. While there is clearly room for  
22 appropriate clinical input, as well as other

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 relevant evidence in the discussion of an OPC  
2 development, the fundamental developmentation  
3 of OPC must be data driven. Rigorous and  
4 scientifically valid methodologies should be  
5 developed and employed in the derivation of  
6 any OPC for use in the medical device and  
7 process.

8 This implies that OPC must be  
9 derived from recognized and generally complete  
10 historical data sets. Further, there should  
11 be a data provision for periodically  
12 evaluation and updating the OPC based on more  
13 recent experience and data. Note that  
14 different OPCs shall be developed for  
15 different patient population and different  
16 indications.

17 Here is the checklist on whether an  
18 OPC can be used for a particular device. It's  
19 much known about the natural history of the  
20 device. Is the patient population well  
21 understood? Are the extensive experience and  
22 history? Is there stable and well-known

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 standard of care? Is the ancillary technology  
2 stable? Are there no significant new  
3 questions of the effectiveness? Is there  
4 consensus among all relevant communities? Are  
5 significant positive results expected?

6 If the answers for these questions  
7 are yes, OPC may be a good option to choose.

8 Regarding the use of an OPC for the  
9 endometrial ablation devices with the elective  
10 use, we believe that the following barriers  
11 are significant. A new indication is targeted  
12 for a new subject population, women with  
13 normal menstrual bleeding. It is different  
14 from the current patient population, women  
15 with menorrhagia.

16 There are no studies that have been  
17 conducted for the new indication. Therefore,  
18 we know of no valuable data that can be used  
19 to develop an OPC. These are the biggest  
20 barriers for considering an OPC here. Either  
21 you can say that other limitations for an OPC  
22 presented above may also apply here.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS  
1323 RHODE ISLAND AVE., N.W.  
WASHINGTON, D.C. 20005-3701

1 Therefore, we don't think that the use of an  
2 OPC is an applicable option for endometrial  
3 ablation devices with the elective use.

4 This is the end of my presentation.

5 Thank you very much. Now, I'll turn the  
6 podium back to Veronica.

7 MS. PRICE: So if we cannot  
8 identify an appropriate control group and an  
9 OPC is not applicable in this situation, then  
10 we may consider setting a clinically derived  
11 target success rate. This rate can be used to  
12 develop a statistical hypothesis from which a  
13 sample size can be derived. We will be  
14 interested in the Panel's input on what this  
15 target success rate might be. This is a  
16 subject of one of our discussion questions.

17 The last study design issue that we  
18 would like the Panel to consider is the issue  
19 of follow-up. The previous studies of  
20 endometrial ablation require a 12 month  
21 follow-up on all study subjects in the pre-  
22 market period with an additional 24 months in

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 the post-market period for a total of three  
2 years of follow-up. We're interested in the  
3 Panel's input on the follow-up regimen for  
4 this new study population.

5 For some this new indication raises  
6 ethical concerns. So I would like to spend  
7 the next few moments of my presentation this  
8 morning discussing ethical considerations and  
9 how they may be applied to a clinical  
10 investigation of endometrial ablation devices  
11 for elective use.

12 Although this is something that I  
13 will only touch upon briefly today, it is an  
14 important issue to raise here, since this  
15 proposed elective use of endometrial ablation  
16 represents a departure from our typical  
17 evaluation of obstetric and gynecology devices  
18 in which a medical device is being used to  
19 treat an abnormal condition.

20 We are here this morning to talk  
21 about an elective or a cosmetic use of a  
22 medical device. Although FDA has and does

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 review medical device applications for  
2 cosmetic use, it is not something that we have  
3 a lot of experience with in the OB GYN Devices  
4 Branch.

5 I would like to acknowledge Dr.  
6 Sarah Goldkind, who is a senior bioethicist in  
7 the Office of the Commissioner at FDA, for her  
8 guidance in the preparation of the next few  
9 slides. I'm pleased that she has been able to  
10 join us here today.

11 There are four guiding principles  
12 in medical ethics with which you are all  
13 probably familiar: Autonomy, beneficence,  
14 non- maleficence and justice. Since we are  
15 focused on clinical trial design today, as  
16 opposed to commercial application, I will talk  
17 about these principles as they relate to the  
18 issue of this clinical trial design.

19 The first guiding principle is  
20 autonomy of study subjects, which in general  
21 terms is respect for the individual, which  
22 includes individual choice. However, it is

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 important to ask ourselves whether there is a  
2 limit to this autonomy. To that end, I will  
3 be asking the Panel to consider whether this  
4 new indication, which will represent treatment  
5 at the request of the patient, is legitimate.

6 In making this determination, it  
7 may be useful to consider some of the  
8 background materials that were provided for  
9 today's discussion, which included published  
10 literature regarding women's perception of  
11 menstruation and the desire for menstrual  
12 suppression for various lifestyle issues.

13 If the Panel determines that this  
14 is a legitimate study, then we would be  
15 interested in the Panel's thoughts regarding  
16 how ethical principles can be honored and  
17 study subjects protected.

18 In thinking about the ways in which  
19 study subjects might be protected, we may  
20 consider the following: That there is an  
21 informed decision to participate and in this  
22 case perhaps we would optimize that process to

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 include more than one counseling session, a  
2 second clinical opinion, perhaps a  
3 psychological assessment and a study subject  
4 advocate.

5 We also may want to consider the  
6 opportunity for participants to discuss the  
7 treatment with women who have undergone an  
8 endometrial ablation procedure. We want to  
9 ensure that we eliminate coercion in any form,  
10 that we avoid value judgments and that  
11 ultimately respect the individual decision and  
12 choice.

13 The next principle is  
14 non-maleficence, which means that direct harm  
15 should be avoided and risks minimized. This  
16 is the essence of the risk/benefit analysis in  
17 which we want to ensure that there is an  
18 appropriate risk to benefit ratio. In this  
19 case, we are concerned about minimizing the  
20 known risks of endometrial ablation,  
21 minimizing the potential for regret and  
22 minimizing the potential for masking a uterine

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 cancer.

2 In terms of the known risks  
3 associated with this procedure, I believe we  
4 can draw upon the extensive experience with  
5 use of these devices in women with  
6 menorrhagia. Adverse events reported during  
7 the pivotal trials for endometrial ablation  
8 devices were categorized according to the time  
9 of occurrence and the approved device  
10 labeling.

11 In this slide, I have included all  
12 reported adverse events observed during the  
13 two week post-operative period for all  
14 approved endometrial ablation devices. Since  
15 the pivotal trials for endometrial ablation  
16 are small and complications are rare, not all  
17 serious adverse events were observed in these  
18 trials.

19 Through FDA's MAUDE Database, we  
20 are able to get post-market safety information  
21 on these devices. As we become aware of these  
22 events, we are able to work with manufacturers

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 to revise their labeling as needed to include  
2 additional adverse event information.

3 This slide identifies the serious  
4 adverse events that have been noted to occur  
5 with endometrial ablation in the post-market  
6 setting. Unfortunately, our database does not  
7 allow us to determine the rate of occurrence  
8 of these events, but we do know that they are  
9 extremely rare. They include uterine  
10 perforation, urgent hysterectomy, thermal  
11 injury to bowel, bowel resection, post-  
12 ablation tubal sterilization syndrome, thermal  
13 injury to vagina and perineum, infection and  
14 sepsis and it also includes pregnancy-related  
15 complications.

16 Although this device is indicated  
17 for women who have completed childbearing, it  
18 is not a sterilization procedure. The  
19 labeling includes a contraindication for women  
20 who want to become pregnant, because  
21 pregnancies following ablation can be  
22 dangerous for both mother and fetus, as well

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701

1 as a warning that endometrial ablation is not  
2 a sterilization procedure and patients should  
3 be advised of appropriate birth control  
4 methods.

5 In spite of these statements in the  
6 labeling, there have been pregnancies reported  
7 to FDA following endometrial ablation. There  
8 is a discussion question related to  
9 contraception status of study participants as  
10 a result.

11 When we look at the risk/benefit in  
12 this new population, we can consider the known  
13 adverse events from the pre- and post-market  
14 experience in women with menorrhagia. We also  
15 need to consider the potential for masking a  
16 uterine cancer. As indicated in the ACOG  
17 Practice Bulletin, this is not believed to be  
18 a likely issue in women treated with  
19 menorrhagia. We would be interested in the  
20 Panel's input on whether it is more of a  
21 concern in this population. This is the  
22 subject of one of our discussion questions.

**NEAL R. GROSS**

COURT REPORTERS AND TRANSCRIBERS

1323 RHODE ISLAND AVE., N.W.

WASHINGTON, D.C. 20005-3701