

**SUMMARY MINUTES**

**THE OBSTETRICS AND GYNECOLOGY DEVICES PANEL**

**MEETING**

**OPEN SESSION**

**December 14, 2007**

Hilton Washington D.C. North

Gaithersburg, Maryland

**Obstetrics and Gynecology Devices Panel Meeting  
December 14, 2007  
Attendees**

**Acting Panel Chairperson:**

Marcelle Cedars, M.D.  
University of California  
San Francisco, CA

**Voting Members:**

Paula Hillard, M.D.  
Stanford University Medical Center  
Stanford, CA

Howard Sharp, M.D.  
University of Utah  
Salt Lake City, UT

**Consultants:**

Ann Davis, M.D.  
Tufts-New England Medical Center  
Boston, MA

Melissa Gilliam, M.D., M.P.H.  
University of Chicago Medical Center  
Chicago, IL

Herbert Peterson, M.D.  
University of North Carolina  
Chapel Hill, NC

Kathleen Propert, Sc.D.  
University of Pennsylvania, PA

Susan Ramin, M.D.  
University of Texas  
Houston, TX

Nancy Sharts-Hopko, R.N., Ph.D.  
Villanova University  
Villanova, PA

Russell Snyder, M.D.  
The University of Texas Medical Branch  
Galveston, TX

Phillip Stubblefield, M.D.  
Boston Medical Center  
Boston, MA

**Industry Representative:**

Elisabeth George  
Philips Medical Systems  
Newton, MA

**Consumer Representative:**

Diana Romero, Ph.D., M.A.  
City University of New York  
New York, NY

**Executive Secretary:**

Michael T. Bailey, Ph.D.  
Food and Drug Administration  
Rockville, Maryland

Elaine Blyskun, Incoming Executive Secretary  
Food and Drug Administration  
Rockville, Maryland

**FDA Representative:**

Nancy Brogdon  
Food and Drug Administration  
Rockville, Maryland

## CALL TO ORDER

**Chair Cedars** called the open session of the meeting to order at 9:20 a.m. **Executive Secretary Bailey** read the conflict of interest statement. All members were found to be in compliance, and no waivers were issued. **Mr. Colin Pollard**, Chief of the Obstetrics and Gynecology Devices Branch, introduced the day's meeting, which would include an update on post-approval studies (PAS), a review of the PAS experience of an approved PMA, and an introduction to elective endometrial ablation to terminate menses.

## PAS UPDATE

**Dr. Danica Marinac-Dabic**, chief of the Epidemiology Branch of the Office of Surveillance and Biometrics, said that CDRH has made a commitment to enhancing the PAS program by enhancing rigor, establishing accountability, building PAS information management systems, bridging post-market knowledge with pre-market device evaluation, and increasing transparency. She gave an update on CDRH activities, including the recent development of the CDRH Post-Approval Studies Program and ongoing OB/GYN PASs.

Since the transfer of oversight responsibility to the Office of Surveillance and Biometrics (OSB), OSB has developed an electronic tracking system for post-approval commitments. Some fundamental changes in the review process are that an epidemiologist is now assigned to each PMA review team, a PAS protocol or outline is finalized at the time of PMA approval, and the study proceeds by agreed-upon timelines. The epidemiologist leads the PAS design, works with sponsors, attends panel meetings, and leads the review of PAS reports.

The PAS guidance document was issued in 2006, and one minor revision was issued in 2007. The document defines reporting status expectations and definitions for the sponsors. The FDA/FDLI PAS Conference was held in May 2007. The tracking system is publicly available on the website, and the PAS webpage is linked to the PMA database. Panel PAS updates at all future meetings will include both general updates and in-depth updates presented by the sponsors.

There are three ongoing PAS studies in the OB/GYN area that have been initiated since 2005: LUMA, Essure, and Thermachoice. All three studies are observational, single-arm studies. FDA and the sponsors had reached agreement on the PAS protocols for two of these devices at the time of PMA approval. For the other, an outline of the PAS protocol was agreed upon. One report was received overdue in 2007. The other two PMAs had not had a report due yet. One study is on hold and two are pending initiation.

The vision for the future in PAS is to answer the important post-market questions with good, science-based studies that are timely, accurate, and useful. Reports should be clearly identified and effectively tracked. Stakeholders should be kept apprised, and collaboration is stressed throughout. With proactive action, enforcement options will rarely be needed.

## **OPEN PUBLIC HEARING**

Chair Cedars opened the floor for the public comment. Seeing none, she invited the Sponsor's presentation.

## **PAS SPONSOR PRESENTATION**

**Nadir Alikacem, Ph.D.** spoke for InSightec on the ExAblate 2000 System's PAS. He commented on the seamlessness of the PAS process. The ExAblate System is based on thermal ablation, using MR-guided focused ultrasound, which allows planning, real-time telemetry, and feedback on the ablation of targeted tissue, uterine fibroids. Post-treatment evaluation is done while the patient is still on the table. The PMA was approved in 2004, with the conditions of approval and a PAS.

The Sponsor was responsible for three major groups. Group A, 109 patients, were from the pivotal study, controlled against hysterectomy. Group B was a continued access study of 160 patients. The post-approval population, Group C, was 73 African American patients treated following the labeling guidelines. The groups were treated under different guidelines, which caused variations among the groups. Group B's guidelines changed during the continued access study.

One important element is the minimum distance to the serosa, 1.5 cm in Groups A and B1. In a 6cm fibroid, that allows less than 50 percent ablation. In post-PMA follow-up, that restriction is gone, so there is a thermal dose escalation. The Sponsor has been reporting on the analyses of dose escalation and durability of the treatment.

The safety profile of the African American patients treated post-PMA with the increased guidelines shows no adverse events not previously identified. The safety profile has not changed considerably from the previous profile. The African American study shows a slightly higher symptomatology compared to other groups, but that would be expected from the mean symptoms at baseline. As for efficacy, the post-PMA groups with the increased doses showed significant decreases in alternative treatments at 12, 24, and 36 months, compared to Groups A and B1. .

Though the protocol called for patients that are family complete, pregnancy was monitored. From all cohorts, a total of four patients became pregnant. All carried into the third trimester, three had vaginal delivery, and one patient with a history of c-sections had a c-section. The average birth weight was 3398 grams, and there was one postpartum complication: a baby with a collapsed lung who was in ICU for 2 days.

The Sponsor said the overall safety profile was acceptable. There was no significant relation between dose escalation and safety profile, but efficacy was dose-dependant, and the guidelines on patient treatment are reflected in the outcomes.

## **PAS FDA PRESENTATION**

**Nilsa Loyo-Berrios, Ph.D., M.S.** of the Epidemiology Branch presented FDA's position on the ExAblate 2000 PAS. ExAblate 2000 is a noninvasive thermal ablation device that is integrated with the MRI system. It is indicated for perimenopausal women with symptomatic uterine fibroids who desire a uterine-sparing procedure and contraindicated in women who should not undergo magnetic resonance imaging or if the clinician cannot

avoid having important structures in the path of the ultrasound. Patients must have completed childbearing. The PMA was approved in October of 2004 with the conditions of approval being 3 year follow-up of the premarket cohort for safety and effectiveness and a PAS to enroll a new cohort of African American women and follow them through 36 months.

In the pivotal cohort, 47.7 percent of dropouts were due to a second Exablate or an alternative treatment. Due to re-consenting patients for a longer follow-up than originally planned, 25.7 percent of patients were lost to follow-up, so 26.6 percent of patients have 36-month data. The continued access cohort is ongoing, and 36 month data is available for 18 percent of the patients. Additional treatment is the reason for exclusion in 41.2 percent of patients. The 4 pregnancies were also excluded from follow-up. In the PAS cohort, 14 percent of patients were excluded due to additional treatment, none have 36-month data, and 71.2 percent are undergoing follow-up. Overall, of 342 total patients, 16.7 percent of patients have 36 month data, 37.4 percent needed a second or alternative treatment, and 28.1 percent are still being followed.

Each cohort was treated under different guidelines, mostly the percentage of the fibroid treated, the volume allowed to be treated, allowed treatment duration, restricted distance to the endometrium and serosa, restricted distance to fibroid capsule, and whether or not a second treatment was allowed within the first two weeks. Until April of 2004, the guidelines allowed 33 percent of the fibroid to be treated, as opposed to 50 percent after April. The extended guidelines allowed 180 minutes of treatment, as opposed to 120 minutes in the restricted guidelines. The extended guidelines allow a second treatment within two weeks. The pivotal cohort and the first 96 patients of the CAS (B1) were treated under the limited guidelines. The B2 patients were treated under extended guidelines, and the PAS cohort was treated under the commercial guidelines, which are similar to the extended guidelines.

The preliminary efficacy results show main symptom severity QOL effectiveness within six months and apparent sustained benefit for all groups, though the results only represent patients in which the first ExAblate was successful. The preliminary results for fibroid regrowth show a decrease over time. The African American cohort shows a slight increase at six months. The latest report data shows no new adverse events in the continued access or pivotal groups. In the postmarket cohort, there have been no device-related deaths, life-threatening injuries, permanent injuries, acute hospitalizations, or device-related emergency interventional procedures. The most common adverse events were pain and discomfort, 1.9 per 100 patient months, and urinary adverse events, 1.3 per 100 person months. The overall incidence for nonsignificant anticipated adverse events was 5 per 100 months. Most of the adverse events were mild and were resolved in less than two weeks. The rate of alternative or second Exablate treatments increases in the first six months and decreases over time.

The device was contraindicated for use in women who intended to become pregnant, and none have occurred in the pivotal or PAS cohorts. In the new PAS cohort, 6 of the 10 patients with a history of c-section experienced adverse events, three of which were classified as severe.

Overall, there treatment effect in the first 6 months post-treatment seems to be sustained. The data is acceptable with the market safety profile. The postmarket rate of additional treatment is lower for the postmarket cohort. The cohort is ongoing.

**Dr. Loyo-Berrios** concluded that ExAblate is a non-invasive option for treatment of uterine fibroids. The follow-up of the premarket cohorts provide a good estimate for the need of additional treatment for women treated under the limited guidelines, and the follow up of the postmarket cohort provides data to evaluate whether or not the need for additional treatments is decreased. African-American women known to have high prevalence of uterine fibroids, and the data may not be generalizable to other races.

She opened the floor for questions. **Dr. Stubblefield** asked why re-treated patients were not followed. Dr. Loyo-Berrios said the study was designed to represent the effectiveness of the first treatment. Dr. Alikacem said that safety profiles were taken from the patients who left the study at the time they exited the study. Both alternative treatments and second ExAblate treatments were considered treatment failures.

**Dr. Sharp** asked about following patients lost to follow-up. Dr. Alikacem said the Sponsor tried to contact each lost patient three times and sent them certified letters.

**Dr. Zaino** said the PAS cohort is lower in fibroid size and adverse events than the pivotal study. Dr. Alikacem said the average volume in the PAS cohort was larger than in the pivotal study. **Chair Cedar** asked the Sponsor to look at the relationship between volume and safety.

**Dr. Hillard** asked about patients who became pregnant after the procedure. Dr. Loyo-Berrios said that the indications and the labeling clearly contraindicate women who want to become pregnant. Dr. Alikacem said all trials emphasized the point and that it was in the information for prescribers and the patient information booklet. **Dr. Hillard** noted that the information was not on the Sponsor's website. Mr. Pollard asked about the labeling and training program. Dr. Alikacem said that the training has information for prescribers that includes all pivotal study contraindications and extensive training for safe operation. Ms. Brogdon said the language, "for whom childbearing is complete" is in the indications and should be in the advertising.

## **FDA PRESENTATION: ENDOMETRIAL ABLATION**

**Veronica Price**, a reviewer in the Obstetrics and Gynecology Device Branch, presented on endometrial ablation for cessation of menses in premenopausal women for whom childbearing is complete. The Panel had been provided with background information, and FDA sought Panel input on the key classical design issues.

FDA has approved 5 endometrial devices for ablation of the endometrial lining in premenopausal women with menorrhagia for whom childbearing was complete. The safety analyses were based on information obtained from clinical trials and in one case information on commercial use of the device outside the U.S. The effectiveness analyses were based on reduced uterine bleeding. The PBLAC (Pictorial Blood Loss Assessment Chart) scoring system was used. All but one approved pivotal study for endometrial ablation required a score of 150 or higher for inclusion. The definition of success required a score of 75 or lower at 12 months. Amenorrhea was a secondary endpoint, defined as a score of 0 at 12 months. There was a range in amenorrhea rates from 14 to 55 percent in the experimental arms, compared to 25 to 44 percent in the surgical control arms. Rates were stable over 3 years of follow-up.

The issue before the Panel was the elective use indication for women with normal menstrual cycles and the Panel's opinion on inclusion and exclusion factors, including age, permanent sterilization, and other factors. With the new population, cessation of bleeding or amenorrhea is one definition of success. The other is an endpoint of amenorrhea and spotting. The definition of spotting then becomes an issue for the Panel. Additionally, FDA sought guidance on a timepoint for success, as well as a QOL endpoint. There are no existent devices or drugs approved for permanent cessation of normal menses, so FDA seeks guidance on a proposed single-arm study design with a target success rate.

**Dr. Xuefeng Li** explained why FDA does not believe an OPC (Objective Performance Criteria) is appropriate. An OPC is a fixed target value used to evaluate safety and effectiveness and is used as a surrogate for traditional control groups. While trials using OPC are generally less burdensome, they share the limitations of non-randomized control trials with historical controls. It is difficult to develop an OPC from literature or a different patient population, and there are numerous questions of comparability and validity. OPC development should be data-driven. It should be developed from recognized and complete historical datasets and periodically updated. For the elective use of endometrial ablation devices, a new indication is being targeted for a new subject population: women with normal menstrual bleeding. There are no studies and no data for the new indication.

**Ms. Price** said that without an identifiable control group or an applicable OPC, a clinically-derived target success rate could be used to develop a statistical hypothesis from which a sample size can be derived.

The final study issue was follow-up. Previous endometrial ablation studies required 12 months follow-up pre-market and an additional two years post-market. FDA sought Panel opinion on the follow-up regimen for the new population.

The indication raises ethical considerations. The OB/GYN branch is not experienced with elective or cosmetic use of devices. The four guiding principles of medical ethics are autonomy of subjects, beneficence, non-maleficence, and justice. If the Panel determines that the study is legitimate, then FDA seeks Panel guidance on honoring ethical principles and protecting subjects. Protections can include counseling, second clinical opinions, psychological assessments, study subject advocates, or for participants to discuss the treatment with a woman who has undergone endometrial ablation. The principle is to eliminate any coercion and respect individual choice.

Non-maleficence can be ensured by an appropriate risk/benefit analysis and by minimizing known risks. Adverse events associated with endometrial ablation in women with menorrhagia can be gathered from the pivotal studies used to support PMA approval and the MAUDE Database. Serious adverse events are rare, but they include uterine perforation, urgent hysterectomy, thermal injury to the vagina and perineum or bowel, bowel resection, post-ablation tubal sterilization syndrome, infection, and sepsis. There are pregnancy-related complications, but the device is indicated for women who have completed childbearing, though it is not a sterilization procedure. There is also a danger of masking uterine cancer. There is a potential for regret, which can be minimized by enrolling sterilized subjects; however, this raises the risk of post ablation tubal

sterilization syndrome (PATSS). Limiting enrollment to older women would minimize regret but limit the generalizability of the data. These risks must be balanced against the benefit, which is a lifestyle preference. To ensure justice, the patients should not be exploited. The study will require careful consideration of internal issues, applicability of OUS data, and ethical issues. She encouraged sponsors to confer with FDA before engaging in OUS studies.

## **OPEN PUBLIC HEARING**

Chair Cedars read the public hearing statement, encouraging speakers to disclose financial interests.

**Dr. Arthur McCausland** said he had no conflicts of interest. His presentation was on long-term complications of endometrial ablations. He directed the Panel to his article in the Journal of Minimally Invasive Gynecology. He said that long-term complications include central hematometra, cornual hematometra, PATSS, retrograde bleeding, and potential delay in the diagnosis of endometrial cancer. The goal of total or global ablation is to destroy the entire endometrium. Removing the endometrium exposes the myometrial walls, which collapse upon each other and grow together, causing intrauterine contracture.

The Essure/ThermaChoice HSG study was stopped due to severe scarring, and the NovaSure HSG study showed that intrauterine scarring increased over time after ablation. Both first and second generation ablations cause significant uterine scarring. The contracture and scarring can trap blood or endometrium in the upper fundal cornual areas or intramural oviduct above the scar. In 300 uteri, endometrium was found in the intramural oviducts of 25 percent of total ablation patients. In MRI of the uterus, endometrial tissue was detected in 95 percent of total ablation patients, usually in the fundal and cornual regions. Cornual hematometra was found in 18 percent of patients. In a 10 year followup of 50 patients who had rollerball ablation, 10 percent had cornual hematometra or PATSS, and 33 percent of those with tubal ligation developed PATSS. The ACOG Practice Bulletin on endometrial ablation states that there is a 24 percent hysterectomy rate within four years of resectoscopic or non-resectoscopic total endometrial ablations. Symptomatic obstructive blood takes 2 to 3 years to develop, so follow-up should be long enough to capture that data. Patients should be made aware of the dangers, including the masking of uterine cancer. He called to the Panel's attention a recent article showing hysterectomy in a third of total endometrial ablation patients within five years of the procedure, primarily due to pain.

**Dr. Ellen Sheets** of Hologic, Inc., which markets NovaSure, said that 50 percent or more of premenopausal women would prefer amenorrhea. Oral contraceptives and hormone-eluting IUDs have come to market to suppress menstruation, and these methods have side effects that patients accept. She said endometrial ablation should be made available to women who have completed childbearing and are committed to permanent birth control who seek permanent menstrual cessation. Hologic sought Panel guidance on issues around the design of an elective use clinical trial. First, how to ensure that potential subjects are experiencing normal menstrual flow; second, the extent of QOL data to be

documented; and third, how to measure success, since other methods of menstrual suppression allow for breakthrough bleeding. The sanitary products validated for PBLAC are no longer commercially available, and the absorbency of current products will require modifications to the Higham scoring system. She suggested menstrual diaries. She also noted that the scoring system was designed to identify menorrhagia, not normal menses. Therefore, the PBLAC system should be used to rule women out. She said that women are looking for choices in managing menstruation and that a least burdensome approach should be taken to provide the options.

**Dr. Seth Stabinsky** said he had no conflicts. He said that a patient who comes for menorrhagia and needs sterilization who wants an ablation has to wait three months after the sterilization to be ablated. He asked about the effect of combined hysteroscopic sterilization and endometrial ablation on fertility. He suggested the possibility of concomitant and simultaneous endometrial ablation and hysteroscopic sterilization.

**Todd Sloan** of Boston Scientific, which markets the HGA endometrial ablation device, noted that menorrhagia has a broad definition that goes beyond flow rate. Diagnosis and treatment is a collaborative process between the patient and the physician. He said inclusion criteria should maintain the broad definition of menorrhagia so that patients and physicians continue to have access to numerous options.

## **PANEL QUESTIONS**

- 1) In consideration of the four guiding principles for medical ethics, are there recommendations regarding the conduct of a study for elective use of endometrial ablation such that ethical principles can be honored and study subjects protected?**

**For example, does the panel believe that the following proposals regarding an optimized informed consent process should be applied, especially regarding risk/benefit including disclosure of rare but serious adverse events: >1 counseling session; Second clinical opinion; Psychological assessment; and Inclusion of study subject advocate?**

- 2) FDA recognizes the importance of a well controlled-study for addressing issues such as bias; however, in cases where a control group is not feasible, alternative options need to be considered. One option is a single arm study. What are the panel's opinions regarding the design of a study for this new 'lifestyle' indication with respect to the use of a control group? If the panel believes that there is an appropriate control group for use in this type of study, how should this type of study may be implemented? If the panel believes that there is not an appropriate control group, what is the panel's input on how a target success rate may be derived?**

- 3a) We are interested in the panel's input on the following issues related to study entry:**

To date, a Blood Loss Assessment Chart (PBLAC) to quantify blood loss was used for all pivotal studies of endometrial ablation systems with approved PMAs. The PBLAC score was used as both an inclusion criterion (menorrhagia with PBLAC score  $\geq 150$ ) and a patient success criterion (“normal” bleeding with PBLAC score  $\leq 75$ ). Does the panel agree that study entry for the new indication should include a comparable assessment, i.e., a defined PBLAC score representing “normal” bleeding, e.g.,  $\leq 75$ ? Or, is there an alternate criterion for including women with “normal” bleeding? When the study is completed, should results be stratified based on PBLAC score at study entry?

- 3b) The approved labeling for endometrial ablation devices intended for use in women with menorrhagia includes a contraindication for women who want to become pregnant in the future. The labeling also includes a warning that the use of the device does not achieve sterilization and therefore patients should be advised of appropriate birth control methods. Does the panel think that such an advisory is appropriate in this patient population or should entry into the study require that the patient have a history of permanent sterilization? If the panel believes that permanent sterilization should be a requirement, please discuss the potential for an increased risk of post-ablation tubal sterilization syndrome (PATSS).
- 3c) Given that this procedure is a permanent, irreversible treatment, there is concern regarding patient regret with respect to future child-bearing. What are the panel’s thoughts regarding patient age for study entry?
- 4) The labeling for all approved endometrial ablation devices contraindicates the device for use in patients: who are pregnant or want to become pregnant in the future; with known or suspected endometrial carcinoma (uterine cancer) or premalignant change of the endometrium, such as unresolved adenomatous hyperplasia; with any anatomic condition (e.g., history of previous classical cesarean sections or transmural myomectomy) or pathologic condition (e.g., chronic immunosuppressive therapy) that could lead to weakening of the myometrium; with active genital or urinary tract infection at the time of procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis, or cystitis) or with active pelvic inflammatory disease (PID); a patient with an intrauterine device (IUD) currently in place. Are there any other study exclusions that are warranted based on this new intended use?
- 5) We are interested in the panel’s input on an appropriate primary outcome measure for an elective use study. One option that has been considered is amenorrhea (PBLAC = 0). Another option is a combination of amenorrhea and spotting. If the panel believes that the combined endpoint is more appropriate, should there be differentiation between predictable and

**unpredictable spotting and the use of a pantiliner versus no protection? Are there other options that the panel thinks FDA should consider?**

- 6) Endometrial ablation devices approved for use in women with menorrhagia were based on 12-month follow-up pre-market. What does the panel think is the appropriate time frame for evaluating safety and effectiveness in the pre-market setting for this new indication? In addition, women with menorrhagia were followed for an additional 24-months post-market. What does the panel think is the appropriate follow-up period for patients enrolled in this type of study?**
- 7) As a secondary outcome measure, we would expect sponsors to gather information on quality of life issues. This would typically include a questionnaire that assesses patient satisfaction with the procedure and its outcome. Does the panel think that a more comprehensive questionnaire is necessary for this type of study? Is it necessary for such a questionnaire to be validated in this patient population?**
- 8) We are interested in the panel's opinion regarding how FDA should evaluate the adverse events in the proposed study. Does the panel believe the study design should include a statistical hypothesis for adverse events? Recognizing that serious adverse events are rare and are not likely to be observed in a clinical trial, would it be acceptable to set a target upper limit (e.g., 5-7%) for all procedural adverse events (within 30 days of the procedure)?**
- 9) We are interested in the panel's opinion regarding how FDA should evaluate the adverse events in the proposed study. Does the panel believe the study design should include a statistical hypothesis for adverse events? Recognizing that serious adverse events are rare and are not likely to be observed in a clinical trial, would it be acceptable to set a target upper limit (e.g., 5-7%) for all procedural adverse events (within 30 days of the procedure)?**

Instead of discussing the questions individually, the Panel discussed the issue generally in a manner that touched on the questions. They first discussed ethics, which corresponded to question 1. **Dr. Romero** expressed concern about treating the elective surgery the same as a cosmetic surgery, due to the potential serious adverse events. **Dr. Ramin** spoke of autonomy in terms of fully informing the patient. **Dr. Peterson** said the lack of a medical condition being addressed raises the bar for safety. Regret and short and long-term safety issues should be compared to the benefit. **Dr. Stubblefield** said the burden to show non-maleficence would be high, and how high is unknown, since the long-term complications are rising. **Dr. Hillard** noted that women should be made aware that the procedure will not address all menstrual symptoms, only bleeding. **Dr. Romero** questioned the extent of women's desire for the procedure.

**Dr. Sharp** expressed confusion as to what a normal patient is, since the diagnosis and decision is made with a doctor and the device may already be in use off label. The psychiatric evaluation raised questions as to what psychological issues would be exclusion criteria. **Dr. Sharts-Hopko** noted the difficulty of defining who has completed childbirth. **Dr. Davis** raised the possibility of regret among patients encouraged to undergo this procedure by their employers. Additionally, impartial counselors and impartial second opinions may be hard to regulate. **Dr. Stubblefield** said that the procedure cannot be separated from sterilization.

**Ms. Brogdon** asked for more commentary on the mitigation examples. **Dr. Gilliam** said the last three suggestions questioned the patient's competence and that the psychological assessment was objectionable. The second counseling session was reasonable. **Chair Cedars** said that the counselor can use the second counseling session to assess the patient's understanding of the procedure. **Dr. Zaino** was concerned about how patient advocates would translate into the general population.

The Panel discussion segued into the use of a control group, which corresponded to question 2. **Chair Cedars** said the sterilization issue could go to the control group issue, if there is a comparator that is a contraceptive and induces amenorrhea. **Dr. Gilliam** said a control group is necessary and suggested a Levonorgestrel IUD. **Dr. ProPERT** said that the endpoint will determine an appropriate control. **Dr. Sharp** said that having a control would allow the study to provide comparative data on pregnancy and PATSS as secondary outcomes. **Dr. ProPERT** suggested that patient satisfaction could be an appropriate endpoint. **Dr. Peterson** said that it is difficult to think of an outcome that would not require a comparator, especially when the safety bar is set so high.

The Panel moved to a discussion of study design as concerns outcome, which corresponded to questions 5, 6, and 7. **Dr. Zaino** suggested co-primary endpoints to include bleeding and patient satisfaction. **Dr. Sharts-Hopko** noted that, despite shortcomings of QOL literature, it should be used, together with visual analog scales of satisfaction. **Dr. Romero** suggested a more detailed breakdown of components of satisfaction, and added that a comparison group is necessary.

**Dr. Peterson** said that the trial would have to be designed based on the outcome measures. **Dr. Davis** said one quantifiable endpoint could be based on the reasons patients entered the studies. **Dr. Romero** had stated earlier in the discussion that the endpoints should measure the effect the patient desired and that QOL data should be extensive. **Dr. Gilliam** noted the number of women who needed hysterectomies after the procedure and said that QOL could be a secondary outcome, but the primary endpoint should be the most difficult clinical outcome, which will require a large study.

**Dr. Stubblefield** said the long-interval pill and hormone-eluting IUDs are what women use to control menstruation, and patients will want comparative data, which would require looking at all menstrual symptoms. **Dr. ProPERT** agreed with the need to power the study conservatively. **Dr. Sharts-Hopko** said there are menstrual QOL tools. **Chair Cedars** said the outcomes would be some combination of bleeding and something else. She asked for an endpoint. **Dr. Sharp** said the endpoint should be amenorrhea. **Dr. Snyder** pointed out that the amenorrhea rate was already known and advocated satisfaction as an endpoint. He pointed out that it might be more important to answer

whether or not the study should be done. **Chair Cedars** pointed out that the question was not put to the Panel but noted the Panel's discomfort with the indication. **Chair Cedars** noted the Panel consensus of amenorrhea as the bleeding endpoint, but several positions existed on what should be the primary endpoint.

The Panel's discussion moved to inclusion and exclusion criteria, which corresponds to questions 3 and 4. **Dr. Sharts-Hopko** agreed that women who were sterilized but are still fertile should be included. There was Panel consensus for the patients to have undergone a sterilization procedure, though there was concern that then there would be no data on unsterilized patients. If an unsterilized patient used a contraceptive, that contraceptive may affect bleeding. **Dr. Hillard** noted that if previous sterilization is an inclusion criterion, age is no longer an issue. **Dr. Sharp** noted that excluding patients under 40 means not getting data on younger patients. **Dr. Romero** was in favor of the sterilization inclusion criteria, though she said she was unresolved on the issue. **Dr. Peterson** noted the scientific and ethical difficulty of designing the study, due to the amount of uncertainty.

**Mr. Pollard** agreed that more exploration was needed. Noting that the Panel would not have time to answer every question, he recommended that the Panel, rather than answering each question specifically, give the FDA ideas of where to continue exploring. **Dr. Snyder** reiterated the ethical problem said the duty was to include patients who would not be harmed. Short, mid, and long-term risks must be considered. He noted that the natural progression in later reproductive years is from ovulatory to oligo-ovulatory, to anovulatory, to cessation.

The Panel discussion returned to inclusion and exclusion criteria. **Dr. Hillard** asked about a weight cutoff for the group. **Chair Cedars** reiterated the risk of pregnancy and pointed to the availability of IUDs and OCPs. **Ms. George** suggested a comparison to elective laser surgery. **Chair Cedars** commented that if sterilization were not an inclusion criteria, alternate contraception would be needed, which begs the question of another control group. **Mr. Pollard** noted that there are oral contraceptives that are used for menses suppression that could be a control arm, though if it were randomized, that would be more difficult due to one being permanent, the other not. **Dr. Snyder** noted that the Levonorgestrel IUD provides protection against pregnancy, bleeding, and endometrial carcinoma, as opposed to endometrial ablation, which only protects against bleeding.

**Dr. Stubblefield** supported control groups but noted that it introduced complexity to the inclusion and exclusion criteria. He said obese women probably should be included due to their bleeding problems, but those women are at increased risk for thrombosis with oral contraceptives.

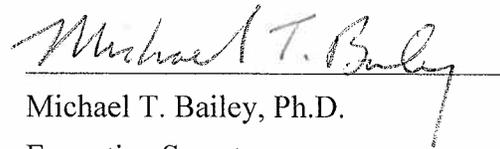
**Mr. Pollard** asked for comments on masking the diagnosis of uterine cancer, which corresponded to question 9. **Chair Cedars** said anovulatory patients should be excluded. **Dr. Zaino** added patients with Lynch Syndrome patients should be excluded. **Chair Cedars** noted that obese patients may be those most in need of non-hormonal menstrual cessation. **Dr. Zaino** suggested endometrial sampling to exclude pathology.

**Chair Cedars** raised the issue of validating QOL questionnaires for the population. Dr. Probert said that only a trial would validate the questionnaire. There was Panel consensus that the threshold for adverse events would be lowered, since the procedure is elective.

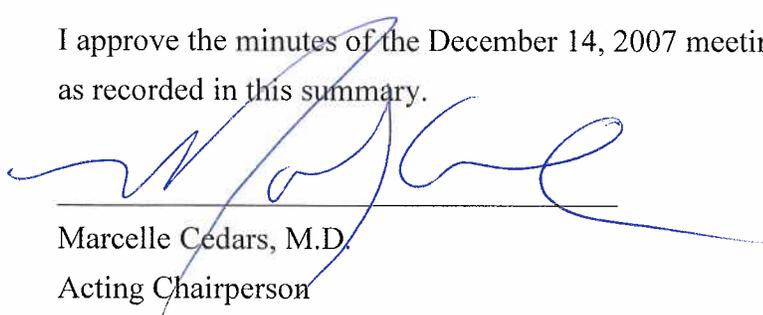
## ADJOURNMENT

**Chair Cedars** said that the Panel discussion had addressed all of the discussion questions and asked if FDA required further input. **Ms. Brogdon** agreed that all questions had been addressed, and Chair Cedars concluded the meeting at 1:18 p.m.

I certify that I attended this meeting of the Obstetrics and Gynecological Devices Panel on December 14, 2007, and that these minutes accurately reflect what transpired.

  
Michael T. Bailey, Ph.D.  
Executive Secretary

I approve the minutes of the December 14, 2007 meeting as recorded in this summary.

  
Marcelle Cedars, M.D.  
Acting Chairperson

***Summary prepared by***

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