

SUMMARY MINUTES

THE OBSTETRICS AND GYNECOLOGY DEVICES PANEL

MEETING

December 13, 2007

Hilton Washington D.C. North

Gaithersburg, Maryland

**Obstetrics and Gynecology Devices Panel Meeting
December 13, 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:

Ralph D'Agostino, Ph.D.
Boston University
Boston, MA

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

Michael Diamond, M.D.
Wayne State University
Detroit, MI

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
Philadelphia, 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

Dr. Cedars called the meeting to order at 8:02 a.m. and noted the presence of a quorum. The purpose of the meeting was to make a recommendation on PMA P070022, the Adiana Transcervical Sterilization System from Hologic, Inc. **Executive Secretary Bailey** read the conflict of interest (COI) statement. All members were in compliance, and no waivers were issued. He then read the appointment of temporary voting members. Drs. Ramin, Zaino, Davis, Sharts-Hopko, Stubblefield, Propert, and D'Agostino were appointed temporary voting members and Dr. Cedars temporary chairman by Dr. Schultz. Dr. Gilliam was appointed by Dr. Lutter.

OPEN PUBLIC HEARING

Chairman Cedars read the public hearing statement, urging disclosure of financial interests.

Amy Gallagher spoke on behalf of the National Association of Nurse Practitioners in Women's Health (NPWH) and disclosed that Hologic had provided funding to NPWH. Of the Adiana device, she said that the design and composition of the implant prevents complications and metal allergies and does not act as a barrier to future non-invasive gynecological procedures.

Dr. Barbara Levy, a clinical consultant for Conceptus, expressed concerns about the device in the areas of safety, effectiveness, and physician training. The safety concerns were application of RF energy to the endosalpinx, difficulty of detecting perforation, risk of hyponatremia, and the number of ectopic pregnancies. Dr. Levy said that the device's effectiveness rate is cause for concern, especially at four years. It is difficult to determine that the tubes are occluded. Due to variations in skills and equipment, there should be didactic and hands-on training. Transvaginal ultrasound should be used for the localization of the matrix and there should be training on HSG (hysterosalpingogram) performance and interpretation. She said the device should only be approved if it is as effective, safer, or more tolerable than existing therapies.

Cindy Domecus, a consultant to Conceptus, commented on her previously-submitted written remarks. She said that the labeling for the device should comply with the FDA's Contraceptive Labeling Guidance Document, which requires that the device's pregnancy rates be compared to the Essure System, the most similar device. She said that the labeling should include pregnancy rate calculations to reflect all contraceptive failures, including failures due to improperly positioned devices. The labeling should duplicate the level of screening at which the failure rates were established: two transvaginal ultrasounds and dual HSG review. She added that labeling for the system should not include unsubstantiated claims about the "natural uterus" or unsubstantiated claims relative to Essure. Claims about compatibility with IVF, endometrial ablation, or other intrauterine procedures should only be permitted after the data has been approved by the

FDA. She said that the draft labeling should include data on ectopic pregnancy or hyponatremia in the adverse event tables.

Dr. Beth Jordan of the Association of Reproductive Health Professionals (ARHP) urged the board to look favorably upon the PMA. She said that making safe, new, and effective contraceptive technologies available and training providers is vital to helping family planning, and women will benefit from having several safe and effective options.

SPONSOR PRESENTATION

Adam Savakus introduced the sponsor presentation and gave an overview of the device development. The Adiana technology has been in development for over ten years. Patient enrollment in the EASE trial began in 2002, and the last EASE treatment was in 2005. The PMA was filed in August of 2007. Clinical follow-up on the trial is ongoing. The proposed indication was: “The Adiana Transcervical Sterilization System is indicated for women who desire permanent birth control (female sterilization) by occlusion of the fallopian tubes.”

The device uses a two-step transcervical approach to permanent contraception. The first step is the creation of a controlled thermal lesion within the intramural portion of the fallopian tube. The second step is the placement of a porous polymer implant (the matrix) within the lesion, resulting in tissue ingrowth and tubal occlusion. Placement in the intramural portion of the fallopian tube avoids difficulties related to navigating the isthmic portion of the fallopian tube.

The System consists of the RF generator and the single-use, disposable Adiana delivery catheter. The generator’s menu-driven interface guides the user through the procedure. The position detector array (PDA) indicates when the catheter is in contact with the fallopian tube. There are no user-adjustable outputs. The tip of the catheter contains the RF array, the PDA sensor, and the implantable matrix. The matrix is 3.5x1.6 mm, and its porous surface makes tissue in-growth possible.

The development studies included *in vitro*, animal, and human peri-hysterectomy, post-hysterectomy, and access studies. The *in vitro* studies on extirpated uteri allowed the development of the catheter and RF array and fine-tuning of the generator. The animal studies looked at ingrowth and tubal occlusion, allowing improvement of the implant design and pregnancy prevention potential. The peri-hysterectomy studies helped characterize the RF lesion and evaluated matrix placement. The pre-hysterectomy studies evaluated tissue in-growth and tubal occlusion. This study showed the expected response at 3 months with no adverse events or complications. The access study assessed the ability to place the device in a representative patient population.

Thierry Vancaillie, MD, FRANZCOG, discussed the procedure and mechanism of action. The biology of biomaterial implants goes back to the 1960s and is well-studied and well-understood. Upon placement, an acute response occurs, followed by a chronic response. Granulation tissue develops. If there is biocompatibility and the material is non-degradable, fibrous tissue forms. With the device, that healing process is started by the application of RF energy, and the implant is placed in the lesion. Stable fibrous tissue in-growth occupies the pores of the implant, resulting in permanent tubal occlusion. This

mechanism of action was confirmed in the hysterectomy study, in which the tubes and implants were examined at three months. Additionally, during the EASE trial, eight patients underwent hysterectomy. This allowed for examination of the implant and in-growth at four years. Granulation tissue forms and evolves into fibrous in-growth, which integrates the device into the surrounding tissue and is stable over time. There is no evidence of fistulization or chronic inflammation.

The treatment schedule consists of patient counseling (emphasizing the need for follow-up), the procedure itself, and follow-up, which includes HSG. Alternative contraception is necessary until HSG at 3 months. The procedure is performed under local anesthesia. A hysteroscope is placed in the uterine cavity. The catheter is introduced and aligned with the tubal ostium. The surgeon threads the catheter into the tubal lumen until the PDA indicates that the catheter is in place. This is checked with a black mark on the catheter. The RF energy is then activated for 60 seconds, and the surgeon presses the button on the handle to place the matrix. After the contralateral side is done, the patient is monitored for 20 minutes, and then the patient is released. The system is easy, straightforward, and requires minimal cervical dilation. The procedure is well-tolerated by patients, is an outpatient procedure requiring minimal anesthesia, and has a short recovery time and no incisions.

Ted Anderson, MD, PhD, FACOG, FACS, an investigator from the EASE trial, spoke on clinical experience. The study was conducted under an FDA IDE approval as a prospective, single-arm clinical study to enroll up to 650 patients at up to 15 institutions. Roll-out was phased with a pause after the first 150 patients enrolled, to ensure that there were fewer than two pregnancies at 200 women months and that the access rate of the tubes were greater than 80 percent. There was a second evaluation to make sure there were fewer than 5 pregnancies at 1000 woman months. Those criteria were met, and enrollment continued over 2.5 years. The trial's primary endpoint was pregnancy prevention at one year. The study was designed for an 80 percent power to demonstrate a pregnancy rate of less than 5 percent with 95 percent confidence, based on enrollment of 400 per protocol subjects with a pregnancy rate of 2.5 percent. Secondary endpoints looked at the device placement rate, the safety of device placement and wearing, and patient satisfaction and comfort with the device placement and wearing.

Inclusion criteria were fertile women aged 18-45 seeking permanent contraception who were at risk for becoming pregnant and were willing to rely on the system. Exclusion criteria were pre-existing health conditions that would affect the ability to undergo the procedure, prevent compliance to follow-up, and bias post-procedural evaluation. After the procedure, patients underwent a three-month waiting period, during which they relied on an alternative contraception. At three months, tubal occlusion was verified by HSG. When occlusion was demonstrated, patients discontinued alternate contraception and relied on the device for 12 months, the primary endpoint. Patients are followed out to five years.

Of 770 patients enrolled, 143 were enrolled outside of the US. Due to screening failure or voluntary withdrawal, 115 patients were eliminated. Of 655 patients who went to hysteroscopy, 10 were excluded for pathology or procedural criteria, leaving an intent to treat population of 645. The baseline characteristics were diverse in age and ethnicity, and the age distribution was similar to the CREST study.

In the intent to treat population, 95 percent of patients had successful, bilateral placement of the matrix. Failed placements were usually due to uterine anomalies or suspected tubal blockage. Placement success was high across the sites. The mean procedure time was under 12 minutes, and 90 percent were performed in less than 20 minutes. The mean glycine volume used was 1226 cc. No sedation, only topical anesthesia was required in 33.2 percent of the patients; 19.8 percent of the patients were given an anxiolytic and minimal sedation. Mild to moderate conscious sedation was used in 47 percent of the patients. No patient required intubation or general anesthesia.

The most common procedural adverse events were cramping (26 percent) and vaginal spotting (12 percent). The remaining reported events were minor and infrequent, except for a single mild case of hyponatremia. There were no uterine or tubal perforations, no RF-related or placement-related injuries. After the procedure, 98 percent of women reported tolerating the procedure well to excellent, and the mean VAS score was 5.9 out of 100. Within two days, 98 percent of women returned to normal activities, 90 percent within 1 day.

During the 3 month period, 1 patient was lost to alternative contraception failure and 6 lost to follow-up or withdrawal. Of the remaining 604 patients to experience HSG at 3 months, 551 demonstrated bilateral tubal occlusion. 53 had one or more tube patent; 45 of these patients were reevaluated at 6 months, and 19 of them then had bilateral tubal occlusion. This left a total of 570 patients able to enter the efficacy follow-up (94.4 percent of the patients HSG-evaluated, 88.4 percent of the intent to treat population).

During the one-year follow-up, compliance was 97 percent. There were 6 pregnancies in the first year, 3 due to HSG interpretation errors, 3 due to failures of undetermined cause. There were 3 pregnancies in year 2, none in year 3, and one in year 4. The failure rate in the first year was 1.07 percent, meeting the primary endpoint. The failure rate is 0.54 percent if the pregnancies due to HSG misinterpretation are excluded. He concluded the device's effectiveness is comparable to other sterilization methods and superior to contraceptive methods.

Adverse events during the first year of compliance were low. Cramping, bleeding, and dysmenorrhea was found to occur more often in patients who had previously relied on birth control pills and may have been a result of discontinuing birth control pills. Serious adverse events included 2 ectopic pregnancies and one endometrial polyp. Most adverse events were mild and resolved spontaneously. There were no allergic or adverse reactions or infections related to the matrix, and there were no removals. He concluded that the clinical experience demonstrated 16,000 women wearing months with a high placement success rate, that the procedure was well tolerated and had a strong safety profile, and that the device showed 98.9 percent pregnancy prevention at one year.

Amy Pollack, MD, FACOG, FACPM, a consultant to the sponsor, spoke on device's addressing an unmet need and the device's risk/benefit ratio. Because pregnancy, especially unintended pregnancy, carries risk and because half of all pregnancies are unintended, contraceptive options are needed to address a woman's changing contraceptive needs over a lifetime. Female sterilization is among the most widely-used methods, especially in women over 40. Laparoscopic procedures represented an advance

but still carry risks, including risks due to anesthesia and abdominal entry. There is a 1 to 2 percent major complication rate. Transcervical sterilization is a safer, in-office option.

The risks associated with the Adiana System include the general risks associated with hysteroscopy, failure of the procedure to allow reliance (88 percent reliance in EASE), the known risk of regret with all permanent sterilization, and the failure rate of the method to prevent pregnancy. The pregnancy rate was 1.07 percent at one year, meeting the primary endpoint and within the range of the CREST study results and rates remain within the expected range out to 4 years. In EASE, there were 2 ectopic pregnancies out of 10 pregnancies among relying women. They were detected early and treated successfully. In the CREST study, 33 percent of post-sterilization pregnancies were ectopic; ectopic pregnancy is a risk common to all female sterilization procedures.

The benefits of the device are the safe, inert, and biocompatible implant; the stable tissue in-growth; and the device's not extending into the uterus, which means it should not contraindicate future intrauterine procedures. The transcervical approach avoids the risks associated with other methods. The System is easy to use. The procedure is brief and well-tolerated. Throughout the wearing period, there are no adverse device reactions and there is a high level of comfort and satisfaction.

Adam Savakus returned to address the FDA discussion questions, offering the Sponsor's suggested answers. He said a draft training program has been developed, based on the training given in the EASE trial. That plan, as well as draft labeling, was provided to the Panel in written form. The Sponsor plans to follow the EASE cohort out to 5 years and update the labeling.

Chair Cedars opened the floor for questions for the Sponsor. **Dr. D'Agostino** commented that the analysis was based on 554 patients, while the intent to treat population was 645, so the failure rate of the device would be much higher in an intent-to-treat analysis. Mr. Savakus said that pregnancies prior to 3 months were due to the failure of alternative birth control methods, and the device should not be relied upon until the 3 month HSG.

Dr. Snyder asked about the location of the ectopic pregnancies, for more details on the misinterpreted HSGs, and for an explanation of the discrepancy between initial review and local review. Mr. Savakus said that the HSGs were interpreted by investigators, but they went to blinded core lab reviewers, who had the advantage of replaying the video. Dr. Carignan, a sponsor consultant, added that the core review was retrospective and came after the patients began relying on the device. The images available varied. Where the reviewers felt there were significant issues with HSGs or inadequate data to document an occlusion, investigators were asked to repeat HSGs. Future training will include HSG training. Dr. Pollack said that the first ectopic pregnancy was a right isthmic ectopic pregnancy at 7 months of reliance. The second was at 13 months reliance and was resolved by salpingectomy.

Dr. Peterson asked about the length of the procedure resulting in hyponatremia. Dr. Anderson said that the case was a significant outlier. The patient had a 3,000 cc fluid deficit, and most hysteroscopic procedures would be stopped after a 1,000 cc deficit. Fluid management systems were not used throughout the trial. Proper limits of timing and fluid use would prevent this possibility.

Dr. Diamond asked if tubal patency was reassessed in the patients with tubal pregnancy, about the cumulative failure rate of the entire intent-to-treat analysis, about characteristics (such as tubal diameter) of patients with tubal patency, and if collagen staining had been done on patients who later had hysterectomies. Dr. Anderson said there were no clinical predictors of bilateral occlusion or patencies. As the procedure and device move into public hands, HSG follow-up must be stressed. Dr. Victoria Carr-Brendel, a Sponsor consultant, said an immunohistological assessment of the type of collagen was not done but that trichrome staining was used to demonstrate collagen presence in the patients who had hysterectomies. **Dr. Diamond** said that pores may occur during the transition from collagen 3 to collagen 1. Dr. Carr-Brendel said it is most important to stain for epithelium. **Dr. Diamond** noted that rabbit studies may not correspond to human responses, due the difference in tubal size. Dr. Carr-Brendel pointed out that the matrix is designed to expand, and there is no evidence that the matrix is undersized. **Dr. Diamond** further asked about the construction of the matrix. Mr. Savakus said the matrix is one continuous piece of cast silicone rubber.

Dr. Zaino asked if failure to achieve occlusion could be linked to extravascularization of the matrix beyond the tube. Mr. Savakus said that subintimal placement of the matrix had occurred in the pre-hysterectomy group, which was diseased. Dr. Zaino further asked if there were any data on reversing the procedure. Mr. Savakus said there was not. Members had other questions and requests for information, which were addressed by the Sponsor after the lunch break, during the Panel Discussion period.

FDA PRESENTATION

Glenn Bell, PhD, lead reviewer on the PMA, introduced his team and the preclinical review. He began with the history of the PMA review. The pre-IDE was submitted in February of 2002, the IDE in July of 2002. The pivotal trial began in November of 2002, and the last patient was treated in May of 2005. The indications and device description were as the Sponsor presented. There were several changes to the device, including a change during the pivotal trial: the handle design was changed to include a push button, rather than the original thumb slide. The new design was used in 310 patients. Tubal access was approximately the same for the two devices. After the pivotal trial, the push rod and the electrode band spacing were changed. This was to decrease the number of matrix release failures. The foot switch, which actuates the RF generator, was changed to comply with electrical safety requirements. These changes are not expected to change the safety and effectiveness of the device.

The preclinical review consisted of *in vitro* studies, animal studies, mechanical testing, electrical safety and software testing, thermal modeling, toxicological testing, sterilization and packaging, and the shelf life testing. *In vitro* testing in extirpated uteri showed that epithelial ablation varied from 35 to 100 percent, lesion length from 1.28 to 8.58 mm, and lesion depth from 0.33 to 0.73 mm. The relation between these variations in lesion and ablation and any variation in in-growth is unclear. In the rabbit studies, the matrix retention rate was over 95 percent, and in-growth showed a foreign body response. Mechanical testing of the catheter included visual microscopic inspection, dimensional inspection, tensile testing of connectivity and insulation, repeated hysteroscope insertion and removal, compressive loading for tip flexibility, device rotation for torsion on the

handle, testing for the waterproof integrity of the catheter, and testing for heat withstand and actuator release. The matrix was tested mechanically with compression testing, and the implant showed no crevices or tears and indicated the same tensile strength cycled or un-cycled. The catheter passed dielectric withstand and high frequency leakage current testing. The RF generator met international standards for safety and electromagnetic compatibility. The software was tested for hazard analysis, specification requirements, traceability, verification, and validation. The thermal modeling predicted a lesion of 6.88 by 1.3 mm. All patient-contacting materials passed tests for cytotoxicity, irritation, sensitization, system toxicity, and genotoxicity. The catheter was validated to a sterility level of 10^{-6} . The packaging was tested and validated for a 1 year shelf life. Due to being stored in the catheter, a matrix that has been stored does not expand back to specification immediately, but over 24 hours. It is unclear what effect this may have on placement. There are no outstanding review issues.

Julia Carey-Corrado, MD, addressed the clinical review. The FDA review is ongoing, and a labeling review has not yet begun. Literature on transcervical sterilization goes back to 1849. It became mainstream clinical practice in 2002 with the approval of the Essure System. The Adiana PMA is the second PMA for a transcervical device to come before the Panel. The mechanism of action is a controlled thermal lesion combined with a matrix implant. The target placement is at the utero-tubal junction, and the thermal lesion stimulates in-growth. The first of the early clinical studies was the tubal access study, which simulated device placement; success was 93 percent. The peri-hysterectomy studies (128 subjects) showed that the average lesion depth was 0.56 mm, the average length 5.44 mm. There was 93 percent epithelial ablation and a peak serosal temperature of 41.7 degrees. The pre-hysterectomy studies were done outside of the US in 65 patients. The access rate was 87 to 100 percent. Patient tolerance was good, tube occlusion 97 percent. There were 2 adverse events: matrices impinging the wall of the tube. The Sponsor developed a scoring system for tissue in-growth. A slice of tissue, including the matrix, was graded on three quantitative counts (closed vascular spaces, residual epithelial cells, and inflammatory cells) and three graded assessments (giant cells, fibrotic capsule, and necrosis). The system scores ranged from 1-4, better ingrowth being higher. The mean ingrowth score for the pre-hysterectomy study was 2.44.

The EASE Pivotal Clinical Trial was as described by the Sponsor. There were important outcomes that were not identified as endpoints. Of 770 subjects interviewed, there were 645 procedure attempts and 611 placement successes, of which 7 were after repeat procedures. At 12 weeks there were 7 exclusions, one due to pregnancy, and 604 patients went to HSG, of which 551 had bilateral occlusion. At 24 weeks, 19 more had bilateral occlusion. These 570 patients relied on the device for one year, of whom 17 patients were removed from the population, 11 being lost to follow-up: 2 withdrawing voluntarily, 1 terminated, and 3 instructed to discontinue reliance. This left 553 patients to be evaluated at the primary efficacy endpoint. Demographics were well-distributed. Though the use of sedation was minimal, 56.8 percent of US patients received some form of IV sedation. Sedation numbers were lower outside of the US. Other medications were used during the procedure: prophylactic antibiotics in 3.7 percent of patients, anti-emetics in 38.4 percent, and anti-cholinergics in 8.4 percent. By transvaginal ultrasound, 3 matrices appeared to be missing at one week post-placement and another 2 at 12 weeks.

Though the rate of success in placement was around 95 percent, 85.4 percent of the patients relied on the device after HSG at 3 months, 88.3 percent after the additional 19 patients with later occlusion were added. Because some patients will have successful placement without successful occlusion, follow-up is important.

FDA is seeking Panel input on the number of acceptable pregnancies for a sterilization procedure. Five patients became pregnant during the non-reliance period: 1 after successful placement, 1 after a placement failure, and 3 following a diagnosis of patency. Among relying patients, there were 10 pregnancies, 6 in year 1, 3 in year 2, and 1 in year 4. However, the data for years 3, 4, and 5 are incomplete. Of the pregnancies, 2 were ectopic. In one of the pregnancies, the matrices were visible by transvaginal ultrasound, though ultrasound was not done with all pregnancies. Of the pregnancies in the first year, 3 may have been due to errors in HSG or HSG interpretation. Of the year 2 pregnancies, one was ampullary ectopic and occurred 13 months into reliance. The 4th year pregnancy was intrauterine. FDA is looking for risk factors for pregnancy.

Known and potential failure modes include human factors: HSG misinterpretation and possible difficulty holding the catheter stationary during RF and matrix deployment; and tissue response: the possibility to dislodge the device due to secondary forces; and possible patient-specific issues such as comorbidities.

Richard Kotz gave the statistical review of the EASE trial. The observed 1-year pregnancy rate was 1.1 percent with a 1-sided 95 percent exact binomial confidence bound of 2.1 percent, statistically significantly below the objective, 5 percent.

There is missing data in the first year: the 16 patients lost to follow up. However, for the 95 percent confidence bound to exceed 5 percent, 14 of the 16 missing subjects would have to become pregnant in the first year. This is unlikely, so the true rate is most likely still below 5 percent, so the objective is still met.

Dr. Carey-Corrado introduced the Panel discussion questions. For question 2, she highlighted the question of how many sterilization failures (pregnancies) are clinically acceptable in a given year. She offered CREST data for comparison, though she urged caution in comparing the different studies. She noted that devices are approved based on safety and effectiveness, not by comparison to other devices.

Jiping Chen, MD, PhD, MPH, spoke on issues to consider, if the Panel decided a Post-Approval Study (PAS) was necessary. There are three important questions to be addressed by a PAS: what will be the real-world performance of the device, will the device show long-term safety and effectiveness, and is there a need for a postmarket protocol for explant analysis in the event of a hysterectomy?

The Sponsor's proposed PAS protocol is to conduct a prospective, single-armed, multi-center, international study with historical controls. The population will be 625 women, 18-45, who enrolled in the EASE trial and received at least one implant. The 570 women relying on the device will be followed for effectiveness and safety. The 55 patients who received but do not rely on the device will be followed for safety only. There will be yearly office visits out to 5 years. The primary effectiveness endpoint is pregnancy rates at 2, 3, 4, and 5 years, with a hypothesis of 95 percent upper confidence bound for rate lower than 3, 4, 5, and 6 percent for each year respectively. The safety

analysis will be descriptive analyses of adverse events, and the secondary analysis is to compare pregnancy rates against CREST data.

FDA notes that the proposed PAS protocol uses the premarket cohort and would like to hear discussion from the Panel on the possible need to enroll new patients. Second, FDA wonders if the proposed historical control, the CREST study, is appropriate. Third, FDA asked the panel to discuss the adequacy of the length of the proposed follow-up, and finally, FDA asked the Panel to discuss the need for an explant analysis in the event of a hysterectomy. FDA further asked about the need to focus on long-term safety endpoints not addressed by the proposed protocol.

Chair Cedars opened the floor for Panel comments or questions. **Dr. D'Agostino** commented that an intent-to-treat analysis may be impossible. He questioned the target pregnancy rate of 5 percent per year. He noted that the study population was highly motivated, and the rates may not be comparable to rates in the general population. He noted that even within the study the younger patients as a subset do not meet the 5 percent primary endpoint. Mr. Kotz said that the intent-to-treat analysis rate would be higher, but it can't be determined how much higher. He agreed that the younger patients had higher failure rates. **Dr. D'Agostino** noted that the numbers were very unstable. **Dr. Carey-Corrado** said the failure rate of less than 5 percent came from Panel input on a trial for a different device as the rate at which the Panel would be concerned.

Dr. Diamond asked about histological analyses on hysterectomies. **Dr. Willett** said he'd asked for photo micrographs of low-power and representative high-power views of H&E and the trichrome stains. The low-power views showed ingrowth. The high-power views showed fibrotic changes but no pattern of complete disruption of the ingrowth. He noted that the process of preparing slides with a foreign body is difficult. **Dr. Diamond** asked about the change in the catheter design and the possible effect on efficacy. **Dr. Bell** said that the electrode remained within the original specifications and was moved to reduce matrix release failures. **Dr. Sharts-Hopko** asked for any data on the procedure in patients with a pre-existing subclinical infection. **Dr. Carey-Corrado** said she knew of no such data. There were other questions that were addressed after lunch or were redirected to the Sponsor.

PANEL DISCUSSION

Dr. Carey-Corrado addressed the intent to treat versus protocol analyses. She said the primary effectiveness analysis was not based on an intent to treat analysis. Performance in the trial may not reflect real world experience. The complexity of the device precluded a simple intent-to-treat analysis. Effectiveness was judged based on the number of patients told to rely on the device.

Mr. Savakus addressed a question on screening failures. During the screening process, 14 patients were excluded for reasons such as uterine pathology, abnormal uterine anatomy or irregular menses. Five patients were excluded because they became pregnant before using the device. Patients had to be in a monogamous relationship, and two patients had their relationships end. Another patient was contraindicated for sterilization. Other patients simply withdrew from the study. Seventy-five patients withdrew consent prior to treatment.

Dr. Propert asked how much time passed between enrollment and hysteroscopy. Mr. Savakus said that it was often rapid, but it varied, since irregular menses could delay participation. Addressing a question about the shelf life of the matrices, he compared the shelf life of matrices implanted to the pregnancies. He noted that the matrices that had been stored for six months didn't fully expand during the first 24 hours after release, while newer matrices expanded instantly upon release from the catheter. The Sponsor saw no impact on matrix retention. Of the 5 matrices lost during the trial, 2 were expected, due to improper placement. Overall, the lost matrices represent a very small percentage.

Mr. Savakus addressed hysterectomy histology. Of 10 patients in the trial who had hysterectomies, 8 allowed the Sponsor to retain the implanted tissue, and the samples were graded. The hysterectomies were performed for reasons unrelated to the device.

Mr. Savakus addressed a question about band spacing. The specifications are within the tolerance of the original specifications, and the change does not alter RF performance of the device. The change is to reduce failures.

Addressing the questions about pregnancies in the younger population, he noted that younger women are generally at risk for sterilization failure, and in the EASE study, the pregnancies appeared predominantly in the younger patients.

Dr. Carignan spoke on the questions pertaining to the core lab and HSG review. His lab reviewed 734 HSGs from 605 subjects. They found that 93.5 percent of HSGs were adequate to evaluate tubal patency. The lab asked for repeat HSG on 48 HSGs. Of the 10 pregnancies, 3 were due to misinterpreted HSG, 3 due to inconclusive HSG, and 4 in patients for whom the core lab agreed that the HSG was adequate to indicate occlusion. He noted that patient compliance and follow-up are also necessary with the Essure device and with vasectomies.

Dr. Anderson discussed subclinical disease and infection, saying there was no direct evidence of infection. **Dr. Richart** said that inflammation or hyperplasia in the interstitial portions of the fallopian tubes is rare.

Dr. Pollack addressed the question of comparisons other than the CREST study. The Sponsor looked at trials for the Filshie Clip, which had a one-year failure rate of 1.9 per thousand women in one study, 2.5 per thousand in another. They had a 33 percent loss to follow-up. The Hulka Clip also had a high loss to follow-up rate.

Mr. Savakus said that the bilateral placement failures were 3.85 percent in the 18 to 27 age group, 4.55 percent in the 28 to 33 age group, and 7.73 percent in the 34 to 45 age group.

Dr. D'Agostino asked if all subjects were accounted for at 2 years. Mr. Savakus said 1.9 percent of patients were lost to follow-up. **Dr. Davis** asked about the potential of the device being dislodged due to HSGs. Mr. Savakus said pressure was limited to 200 mm of mercury, using a balloon device.

Dr. Zaino expressed confusion as to the number of core lab reversals. Mr. Savakus said that the core lab confirmed the original conclusion in all but 4 cases, though there were 48 cases in which the core lab asked for a second HSG. There were 198 cases in which the core lab had some question, but these questions were all adjudicated. They were often simply requests for more data.

Dr. Diamond asked about the HSG pressure. Mr. Savakus said the pressure was derived experimentally during the pre-hysterectomy studies. **Dr. Diamond** commented

that, when tracked by age, placement failure and pregnancy rates were inversely proportional. Mr. Savakus said more pregnancy is expected in younger populations.

Dr. Gilliam asked about radiologists at the investigational site. Mr. Savakus said HSGs were read by investigators except for at two sites, which used radiologists. **Chair Cedars** asked the age of the three matrixes that missing at one week. Mr. Savakus said they varied in age from 2.4 to 4.2 months. Chair Cedars further asked about perforations in the pre-hysterectomy studies. Mr. Savakus said RF was intentionally delivered to the intramural portion of the fallopian tube, preventing perforation outside of the tubal serosa. The lesion is small, and the catheter is short and deigned to bend before reaching perforation forces.

PANEL DISCUSSION QUESTIONS

Chair Cedars moved to the Panel discussion questions.

1. Is the safety profile of this device clinically acceptable?

Panel consensus was that the safety profile was favorable. However, there were concerns about training in placement and the use of the hypotonic solution as well as training for radiology and the HSG and HSG interpretation.

2. Are the study effectiveness rates for bilateral placement, bilateral occlusion, and pregnancy clinically acceptable?

Panel consensus was that the predefined goals of the study had been met. However, there were three concerns. One is that the HSG should be considered part of the procedure, because the reliance time point doesn't begin until after proof of obstruction or a bilateral occlusion by the HSG. The second concern was counseling patients. The intent to treat analysis was considered important for counseling. The Panel expressed concerns about the generalizability of the data, what will happen in actual use, and long-term effectiveness rates. Dr. D'Agostino added that the generalizability relies heavily on a group the individuals in the study and said that the analysis relied too heavily on too few events. Concerns with the study design.

3. Does the panel believe that the benefits of contraceptive effectiveness, as evidenced by the 1- and 2-year pregnancy rates, outweigh the device risks? The panel may also consider other possible clinical benefits, e.g., hysteroscopic placement instead of laparoscopic placement.

Panel concensus was that if the effectiveness of laparoscopic and hysteroscopic techniques were equivalent, hysteroscopic techniques would be superior due to safety. The question was how much of a loss of effectiveness was tolerable for the increased benefit of the hysteroscopy versus the laparoscopy. Dr. Hillard noted that the expertise affects the outcome. Dr. Peterson noted that the long-term rates of ectopic pregnancy were unknown. The Panel had difficulty with the risk/benefit ratio due to concerns about effectiveness, benefit, and risk of ectopic pregnancy. Chair Cedars said that patients

would have to be counseled on the success rate, and it is important to note the psychosocial cost of a pregnancy. The benefit of no anesthesia during the procedure may be offset by the HSG procedure three months later. Hysteroscopy is safer than laparoscopy, but that risk must be balanced against the increased risk of pregnancy or ectopic pregnancy. The Panel consensus was that the device met the FDA requirements for risk and benefit.

4. Does the panel have any comments on the training plan proposed by the sponsor?

Panel consensus was that the training instructions from the Sponsor were appropriate but that there should be additional information about fluid management and additional information in the training manual about counseling for the physician, not just in the patient information but also counseling and the importance of patient involvement in this particular type of sterilization procedure. The target group for the procedure was important, since younger patients have higher pregnancy and higher regret. That could be a counseling and labeling issue. There was general agreement that the physician should culture for subclinical infections. Though the Sponsor made no decisions based on ultrasound, many Members were uncomfortable with a procedure that does not follow trial design. The Panel did not reach agreement on that issue.

5. Does the panel have any comments on the labeling provided by the sponsor?

The Panel's first issue was that sterilization should be understood not as a procedure but a process consisting of many procedures. Extensive counseling is necessary on the length of the process, the need for alternative contraception, the procedure, immediate risks, and that the treatment is not complete until after the 3 month HSG. Second, the success rate should state the success rate from the time someone begins the process, not just the success rate after bilateral occlusion. Third, there should be a specific statement about ectopic risk and the percentage of pregnancies that are ectopic.

6. Please comment on whether the proposed PAS plan is appropriate to address device long-term safety and effectiveness postmarket.

The Panel supported following the patients currently enrolled for five years. The Panel expressed a desire that enrolled patients be followed further out. Due to concerns about generalizability, the Panel suggested a registry or some way to identify and follow patients who undergo the procedure. There was also support for obtaining tissue specimens from any patients from the trial undergoing a surgical procedure. Follow-up should also follow any attempt to reverse the procedure.

FDA asked for clarification on the control group. The control group could use the Levonogestrel IUD or Essure. Dr. Peterson suggested a cohort study of women seeking sterilization. They would use the device, another transcervical method, a laparoscopic sterilization method, and an IUD, if feasible.

OPEN PUBLIC HEARING

Chair Cedars opened the second open public hearing and reminded the speakers to identify any financial relationships.

Mary Jane Gallagher of the National Family Planning and Reproductive Health Association, which provides health services to low-income and uninsured women and men. The Association supports the Adiana PMA in the interest of providing options to women. She said Adiana is a safe procedure that requires no general anesthesia and minimal time off work.

John Shiarra, MD, of Northwestern University, a former member of the Hologic Data Safety Monitoring Board, gave some background on hysteroscopic procedures to occlude the tubes, which goes back to the 1970s. In the ten years between the first and second international workshop on hysteroscopic sterilization, all approaches had been abandoned due to either safety or efficacy. It became clear that the procedure would require tissue ingrowth or scar formation, as in pelvic inflammatory disease. Essure was the first clinically viable approach to hysteroscopic sterilization. He noted the advantages of hysteroscopic sterilization over laparoscopic sterilization as a less-invasive procedure. He mentioned two theoretical advantages of the Adiana System over Essure: no metal coils in the uterus and no distortion of the uterine cavity.

Arthur McCausland, MD, of UC Davis, reported no financial conflicts. His goal was to inform the FDA of the potential problem of tubal activation after thermal injury to the intermural or proximal oviduct. This was first noted in 1916 during a salpingectomy. A corneal resection injured the intramural oviduct, which caused tubal epithelium to activate and invade the corneal myometrium. This activation can grow into adjacent structures.

He said that the ectopic rate after older types of tubal ligation was 12 percent. However, after a laparoscopic tubal ligation failure, the pregnancy rate was 50 percent. The reason was that older tubes were done in the middle of the tube, as opposed to next to the cornu. Injuring the proximal oviduct close to the cornu can activate that tissue, and this can cause urethral perineal fistula and the sperm can get through and fertilize an ovum in the fimbriated end. However, if you injure the middle part of the tube, you don't see any tubal activation, you just see fibrosis. He suggested serial corneal sections on any hysterectomy specimen taken three or four years after the procedure to check for endosalpingeal blastosis and a painful lesion.

Dr. Seth Stabinski, a former medical director of Adiana with no current affiliation to the company, commented that Dr. McCausland's data did not show causation. He expressed concern about Dr. Diamond's desire to segregate the younger age group. He noted that people were sterilized at much younger ages in the past, and it is burdensome and may be unethical for investigators to recruit patients under 25 years old for sterilization. He noted that patients are afraid of the laparoscopic tubal procedure. He said that it would benefit the patient population and the healthcare providers to have more options.

Cindy Domecus, a consultant for Conceptus, noted that Adiana failure rates had been compared to numerous devices, but not the Essure System, the closest comparator. She said it is the most appropriate control for a post-approval study. She noted that among patients at five years follow-up, Essure's four year failure rate is zero. She pointed out that the Essure PMA was approved with two conditions of approval studies, one for a five-year follow-up, and the other to study placement rates in newly-trained physicians. The sample size was 800 patients. She said the Essure HSG protocol cannot be included in the draft labeling, since the Adiana device is not radiopaque, so the physician cannot look at satisfactory device placement. When Essure was approved, its risk/benefit ratio was justified by the fact that there was no non-incisional method of tubal sterilization available. The Adiana device exists in a landscape where the Essure device exists.

FDA AND SPONSOR SUMMATIONS

The FDA had no further comments. For the Sponsor, **Mr. Savakus** thanked the Panel for its input and guidance, particularly in the area of counseling, patient labeling, and physician training. He expressed a willingness to follow patients from the EASE trial further out but noted that the patients were only consented out to five years. The PAS will be designed through discussions with FDA. He said safety and effectiveness of the device had been demonstrated.

PANEL DELIBERATIONS AND VOTE

Executive Secretary Bailey read the Panel recommendation options. **Dr. Sharts-Hopko** moved approval with conditions. **Dr. Zaino seconded** the motion.

Dr. Stubblefield moved the condition of a PAS as presented by the Sponsor and modified by Panel discussion, to follow the subjects for five years for clinical outcome. **Dr. Davis seconded** the motion. Dr. Diamond suggested follow-up out to ten years. Dr. D'Agostino suggested that new subjects be recruited into the study. **Dr. Stubblefield withdrew the motion.**

Dr. Diamond moved that a condition of approval be that the Sponsor work with FDA to plan a PAS with a 10-year follow-up for the patients from the pivotal trial. **Dr. Ramin seconded the motion. The motion carried unanimously.**

Dr. D'Agostino moved that the PAS include recruitment of new subjects and training of physicians, as presented by the Sponsor. **Dr. Gilliam seconded** the motion. In discussion, Dr. D'Agostino said the follow-up would go out to ten years. Dr. Peterson pointed out that Essure's PAS should not be confused with the Sponsor's and that the Sponsor's proposed PAS physician training had no follow-up. Dr. Chen summarized the proposed PAS: continuation of the EASE trial and explanted tissue in hysterectomy patients out to 10 years, if possible, and determining the design of the PAS with FDA. They were enrolling 45 new physicians and 800 new patients to determine real world experience. Chair Cedars asked whether the experience extended to effectiveness or

merely to placement. Dr. D'Agostino said the purpose of the motion was to make sure the experience being measured was pregnancy. **Dr. Diamond suggested an amendment** to the motion that the motion specified that the study is to be done and to what endpoint but that determining the sample size is left to the FDA and the Sponsor to work out. **Dr. D'Agostino accepted** the amendment. Chair Cedars restated the motion, that there be a PAS that looks at recruitment of new physicians and new patients and follow up with an endpoint of pregnancy and that FDA is involved in the design of that study. **Dr. Diamond seconded** the amended motion. **The motion carried** with all in favor, except for Dr. Probert, who abstained.

Dr. Zaino moved for a post-market protocol for explant analysis in the event of hysterectomy in the patients enrolled in the current study. **Dr. Sharts-Hopko seconded the motion. It carried unanimously.**

Dr. Diamond moved the condition of a perforation study in which there is an intentional perforation and the physician attempts to apply energy, in order to see the effects and whether or not the device will shut off, like it is supposed to. **Dr. Stubblefield seconded** the motion. Dr. Sharp asked what is to be done if it does not work and the device is already approved. Dr. Diamond said FDA could modify labeling or the Sponsor could improve the device. Dr. Diamond said this could be in an animal model or a pre-hysterectomy human model. Dr. Zaino asked that an animal model be specified, for ethical reasons. **Dr. Diamond accepted the friendly amendment. The motion carried** with Dr. Sharp opposed, Dr. Probert abstaining, and all others in favor.

Dr. Peterson moved that the labeling for the patient provider reflect the noted uncertainty regarding long-term effect, pending the effect in the PAS. **Dr. Hillard seconded the motion.** Dr. D'Agostino reminded the FDA of the discussion of the intent to treat population. Ms. George pointed to page 949 of the labeling that indicated that long-term data does not exist. Dr. Peterson wanted the labeling to indicate uncertainty about long-term risk. **The motion carried unanimously.**

Dr. Gilliam moved the condition that the PAS have an active control group, preferably of women electing sterilization, preferably by another transcervical sterilization method. **The motion was not seconded.** Members discussed that they had thought that a control group was part of the prior motions on PAS. **The motion was amended** to require that the PAS have a comparator, to be identified by FDA. **Dr. Peterson seconded the motion, and the motion carried.** Dr. Probert abstained and all others voted in favor.

Dr. Diamond noted that the device failed to meet the primary endpoint in the youngest age group and **moved** that a condition of approval be that approval be limited to patients 28 years of age and older. **There was no second.**

Chair Cedars asked for further conditions. Hearing none, she reiterated the conditions: 10-year followup for existing patients, a new study with new physicians and patients with pregnancy as the outcome, study of tissue explants for enrolled patients with a subsequent surgery, a perforation study, modification of the labeling to address long-term

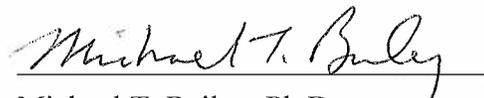
effectiveness, and that the PAS have a comparator group. **She called the motion, which carried 10-3-0, Drs. Snyder, Sharp, and Propert in opposition.**

Chair Cedars had the members explain their votes. **Dr. Snyder** said he voted against approval because the one-year endpoint was too short to predict the results. **Dr. Stubblefield** voted yes, since he felt that the conditions addressed his concerns. **Dr. Zaino** voted in favor due to the evidence of safety and efficacy, though he noted the need for the PAS. **Dr. Ramin** voted to approve with conditions because the Sponsor showed safety and efficacy at one year and the conditions will answer other concerns. **Dr. Davis** voted yes because there were clinically meaningful results. **Dr. D'Agostino** voted yes because the Sponsor carried out the required study, though he would have wanted more data and a different study, the PAS will address his concerns. **Dr. Sharts-Hopko** voted yes with conditions since less invasive contraceptive options are needed. She expressed concern about long-term effectiveness and real-world safety. **Dr. Sharp** voted in opposition due to unresolved efficacy issues that should be resolved before approval, not in PAS. **Dr. Peterson** voted to approve and shared his colleagues' concerns on lack of evidence. He urged vigilance in monitoring the device. **Dr. Propert** voted no due to uncertainty about the risk of high failure rates. **Dr. Diamond** voted in favor, despite concerns, specifically in the youngest age group. However, the age groups were not pre-specified, and the Sponsor met all the specified endpoints. **Dr. Gilliam** voted in favor. She expressed concerns about the study design but noted that the Sponsor had met the requirements and that the PAS would give good information. **Dr. Hillard** voted for approval with conditions and expressed cautious optimism. **Ms. George** noted the difficulty of designing studies and urged FDA to seek data from abroad, where devices are often released earlier. **Dr. Romero** said that the decision was difficult for members and will also be difficult for potential patients. She expressed disappointment that the labeling does not indicate that the intervention is a process rather than a one-time event. **Ms. Brogdon** said that issue would be dealt with, though it was not a condition of approval.

ADJOURNMENT

Chair Cedars thanked the Panel, Sponsor, and FDA. She concluded the first day of the meeting at 5:43 p.m.

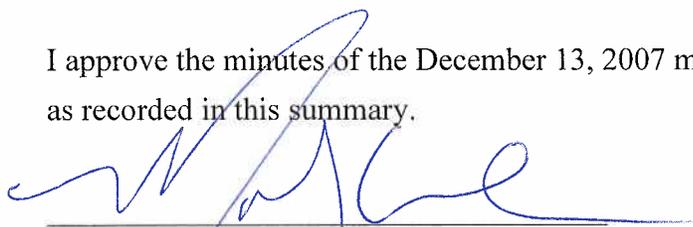
I certify that I attended this meeting of the Obstetrics and Gynecological Devices Panel on December 13, 2007, and that these minutes accurately reflect what transpired.



Michael T. Bailey, Ph.D.

Executive Secretary

I approve the minutes of the December 13, 2007 meeting as recorded in this summary.



Marcelle Cedars, M.D.

Acting Chairperson

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