

**SUMMARY MINUTES  
OF THE  
OBSTETRICS AND GYNECOLOGY DEVICES PANEL**

**OPEN SESSION**

**July 22, 2002**

**Doubletree Inn  
Rockville, Maryland**

**OBSTETRICS AND GYNECOLOGY DEVICES PANEL**  
**July 22, 2002**

**PANEL PARTICIPANTS**

Jorge D. Blanco, M.D.	Chair
Carol Brown, M.D.	Voting Member
Anil K. Dubey, Ph.D., H.C.	Voting Member
Kinley Larntz, Ph.D.	Voting Member
Kleia R. Luckner, J.D., M.S.N.	Consumer Representative
Mary Lou Mooney, R.A.C.	Industry Representative
Kenneth L. Noller, M.D.	Voting Member
Mary Jo O'Sullivan, M.D.	Voting Member
Subir Roy, M.D.	Voting Member
David B. Seifer, M.D.	Voting Member
Nancy C. Sharts-Hopko, Ph.D.	Voting Member
Gerald J. Shirk, M.D.	Voting Member

**FOOD AND DRUG ADMINISTRATION PARTICIPANTS**

Joyce Whang, Ph.D.	Panel Executive Secretary
Collin Pollard	Chief, Obstetrics and Gynecology Devices Branch
Danica Marinac-Dabic, M.D., M.M.Sc.	Office of Surveillance and Biometrics
Julia A. Corrado, M.D.	Medical Officer
Lisa D. Lawrence, R.N.	Lead Reviewer
Gene A. Pennello, Ph.D.	Statistician

**SPONSOR REPRESENTATIVES**

**Conceptus Essure Micro-Insert System (P020014)**

Charles S. Carignan, M.D.  
Vice President, Clinical Research and Medical Affairs  
Conceptus, Inc.

Jay Cooper, M.D.  
Principal Investigator, U.S. Study Team  
Founder and Medical Director, Women's Health Research  
Clinical Assistant Professor, University of Arizona

Cindy Domecus  
Senior Vice President, Clinical Research and Regulatory Affairs  
Conceptus, Inc.

Thomas Wright, M.D.  
Study Histopathologist  
Associate Professor of Pathology and Director, Division of Ob-Gyn Pathology  
Columbia University

Ashish Khera.  
Vice President, Research and Development  
Conceptus, Inc.

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**CALL TO ORDER AND INTRODUCTORY REMARKS**

**Collin Pollard**  
**Chief, Obstetrics and Gynecology Devices Branch**  
**Food and Drug Administration**

**Joyce Whang, Ph.D.**  
**Executive Secretary, Obstetrics and Gynecology Devices Panel**  
**Food and Drug Administration**

Dr. Blanco called the meeting to order at 8:20 a.m. The panel members briefly introduced themselves in turn. Dr. Whang noted that the next scheduled meeting of the panel would be held on October 21–22, 2002. Dr. Whang read appointments to temporary voting status and the conflict of interest statement.

Dr. Pollard welcomed the panel members and announced the issuance of a Level 1 guidance document for adhesion barrier devices, which represents the culmination of a panel meeting held 2 years previously. He expressed the hope that the document would provide further help to those developing products in this area.

Dr. Pollard introduced the first agenda item and gave the panel members some background information. In May 1998, the FDA issued a Public Health Advisory on vacuum-assisted delivery (VAD) devices. Since that time, the advisory has generated a great deal of interest and activity. The Office of Surveillance and Biometrics has continued to work in this area and has taken the initiative to apprise the panel of the results. The following presentation, said Dr. Pollard, would be informational in nature, after which some questions would be entertained as time allowed.

**MEDICAL DEVICE POSTMARKET SURVEILLANCE: VACUUM-ASSISTED DELIVERY DEVICES**

**Danica Marinac-Dabic, M.D., M.M.Sc.**  
**Office of Surveillance and Biometrics**  
**Food and Drug Administration**

Dr. Marinac-Dabic thanked the panel for the opportunity to present the results of the Office of Surveillance and Biometrics's postmarket surveillance of VAD devices. She reported that beginning in 1993 and 1994, the number of reports received by the FDA related to vacuum-assisted delivery devices began to increase. There were an increased number of deaths and the following major types of complications: subgaleal hemorrhage, cephalohematoma, and intracranial hemorrhage. All major VAD device manufacturers and all types of devices were

represented in these reports. Missing from the reports was information on the patterns of use of the devices, the fetal and maternal conditions, and the timing of the injuries. Possible reasons for the increased number of reports of VAD-associated adverse events are an increase in the use of VAD devices, changes in facility reporting, possible under-reporting in previous years, and an actual increased incidence rate of adverse events.

Before issuing the advisory, the FDA reviewed the adverse event reports, the literature on this topic, and the labeling of the devices; engaged in dialogue with device manufacturers and users; and consulted with professional organizations. The Advisory was issued on May 21, 1998, stating the need for caution when using VAD devices. It advised the medical community that VAD devices may cause serious or fatal complications and provided guidance on how to minimize this risk. Post-advisory activities included a review of the adverse event reports and the launching of an FDA-sponsored study (subsequently presented by Barry Schifrin, M.D.; see below). Since 1998, the number of deaths and serious injuries associated with VAD has steadily declined. Meanwhile, the use of VAD has continued to rise.

**Barry S. Schifrin, M.D.**  
**Glendale Adventist Medical Center**  
**Glendale, California**

Dr. Schifrin was the Principal Investigator for Phase I of the FDA-sponsored study, "Adverse Outcomes Associated with Vacuum-Assisted Deliveries." This study was a case-series review on the use of VAD devices. Analysis of the results of Phase II, a case-control study, is currently under way.

A total of 203 cases were enrolled in the study, whose purpose was to evaluate a decision-making apparatus for the use of VAD devices. The study included all patients at 37 or more weeks of gestation in which vacuum extraction was attempted, irrespective of the eventual route of delivery. Numerous obstetric and neonatal features related to process, decisions, outcomes, and behavior were evaluated. Of the 203 cases studied, 106 had more than one application of a vacuum device.

To make sense of the patterns of use of VAD devices, information was collected on the condition and presentation of the fetus, the setting and circumstances of labor, and the history and physical attributes of the mother. Dr. Schifrin noted that, although an implicit notion in the FDA advisory is that adverse outcomes associated with VAD are in fact related to the use of VAD devices, in many cases ischemic injuries are actually not related. Subgaleal and intracranial injuries could be related to VAD, he said, but the most frequent injury found in the study was hypoxemia.

The study found that in many deliveries, attempts were made to speed up delivery and have the mother begin pushing before she was fully dilated. In many cases, fundal pressure was applied not in response to shoulder dystocia, but to help with vacuum extraction.

Only about 60% of the deliveries in the study were accomplished with vacuum extraction. Whereas the usual failure rate of VAD is about 5%, in these cases it was 40% or more. Most of the neonates had low 1-minute Apgar scores, and about 138 (70%) were admitted to the neonatal

intensive care unit. Concerning complications, Dr. Schifrin pointed out that the item of interest was that more than half of these babies had cephalohematoma. Radiologic examination revealed that 15% had subgaleal hemorrhage, the most frequent injury associated with ischemic brain injury.

About half of the babies were injured in the second stage of labor, before the application of vacuum devices. Fetal heart rate tracings showed that in many cases relentless pushing was maintained despite indications of fetal deterioration. Neurologic injuries were indicated by high nonvariable heart rates. In many cases, forceps and vacuum were alternated, sometimes in the presence of profound fetal bradycardia. This scenario, said Dr. Schifrin, was what led to severe neonatal neurologic injury and Erb's palsy, which occurred before the application of VAD devices.

Dr. Schifrin said that the objective of the study was to understand not only the use of vacuum devices but also the conduct of labor in which these devices were applied and the manner in which the injuries occurred. He said the results indicate that injuries were unlikely to be related simply to a problem with the vacuum devices.

### **Questions from the Panel**

To a question of whether he had the opportunity to evaluate the use of vacuum devices in general, Dr. Schifrin replied in the affirmative, noting that the incidence of complications associated with them is quite small. Referring to the "stunning" result that VAD failed in 50% of cases, he noted that when there is no simultaneous preparation for cesarean delivery, as was true in these cases, it becomes necessary to continue efforts at VAD.

Dr. Schifrin was asked whether, in light of the fact that an attending physician must be present when a resident performs a delivery, it will be possible to determine who did the actual application of vacuum in the Phase II study. He replied that medical records are usually inadequate for obtaining this information, and that is it possible that the study may lead to a recommendation to create an ICD-9 code for failed vacuum delivery. He noted that, although there is an ICD-9 code for failed forceps delivery, none of the hospitals called thus far had any record of this code. One physician reported in a deposition that if the delivery was easily accomplished with vacuum, he may not have recorded it in the delivery notes.

Dr. Schifrin was asked whether it will be possible in the Phase II study to differentiate whether problems arose from the vacuum application itself or simply from bad judgment. Dr. Schifrin referred to an instance in the Phase I study in which a vacuum device was applied 16 times, a practice he could not explain under any circumstances. He said that he believes that the problems studied were due to behavior, not the devices, and that nothing in the study suggests that VAD should be done away with.

## **OPEN PUBLIC HEARING**

Dr. Blanco opened the public hearing portion of the meeting, during which presentations were given on the Conceptus Essure Micro-Insert System (P020014).

### **Gabriella Avina, R.N. Martinez, California**

Ms. Avina informed the panel that her financial interest in Conceptus consists of some stock owned by herself and her husband and of payment by the company of her travel expenses.

Ms. Avina has been a Registered Nurse for 16 years in the field of maternal-fetal health. She holds a Master's degree in reproductive health and is married with three children. Ms. Avina recounted her experiences when she and her husband decided not to have any more children. In 1998 she had an intrauterine device placed and became pregnant 7 months later. After the complicated delivery from that pregnancy, her husband underwent a vasectomy, only to find after repeated analyses that his sperm count remained high.

In considering her options for permanent sterilization, Ms. Avina decided to enroll in a clinical trial for the Essure System. She had the devices implanted in October 2000, and it was subsequently confirmed that her fallopian tubes had been successfully occluded. Ms. Avina reported to the panel that the procedure has brought peace of mind, comfort, and security in her relationship with her husband. She said that she spoke for all women in saying that they deserve another contraceptive option.

### **CREST Study Caroline Costello Division of Reproductive Health Centers for Disease Control and Prevention**

Ms. Costello reported on the U.S. Collaborative Review of Sterilization (CREST) study, which was conducted by the Centers for Disease Control and Prevention (CDC) with support from the National Institute of Child Health and Human Development (NICHD). The study was conducted to determine the pregnancy rate among women who had undergone tubal sterilization in nine U.S. sites: Baltimore, MD; Buffalo, NY; Chapel Hill, NC; Honolulu, HI; Houston, TX; Memphis, TN; Sacramento, CA; San Francisco, CA; and St. Louis, MO. Of the pregnancies reported after the procedure, 143 were classified as tubal sterilization failures. (The other pregnancies were classified as luteal phase pregnancies conceived before the sterilization procedure but not identified until afterward, as resulting from reanastomosis or in vitro fertilization, or as unknown status because of insufficient information.) The cumulative probability of pregnancy increased each year after sterilization and was found to be highest for procedures in which the spring clip occlusion method was used and lowest for unipolar coagulation. The pregnancy rate was greatest in women age 18–27 and lowest in those age 34–44 and in black, non-Hispanic women. The rate of ectopic pregnancies was 32.9%, was highest for unipolar coagulation, and increased over time.

The following conclusions were drawn from the study:

- Tubal sterilization is a highly effective method of preventing pregnancy.
- Pregnancy after sterilization occurs substantially more often than is generally reported.
- Tubal sterilization failures occur >1–2 years after sterilization.
- Sterilization method, age, and race-ethnicity can be predictors of sterilization failures.
- All women undergoing tubal sterilization should be informed that pregnancy can occur even very many years after sterilization and that if a pregnancy occurs, there is a high risk that it will be ectopic.

### **CONCEPTUS ESSURE MICRO-INSERT SYSTEM (P020014)**

Mr. Pollard opened the sponsor presentation portion of the hearing and reviewed the panel's function and purpose. The FDA has convened the panel, he said, to obtain their input as experts and will use their recommendations as it moves forward in its review of the application for approval of the Essure implant. He went on to make the following points:

1. The panel's recommendation can take one of three forms: 1) approvable, 2) approvable with conditions, and 3) not approvable. If one of the last two recommendations is made, the FDA would expect recommendations from the panel on what would be needed to make the device approvable.
2. Valid scientific evidence, safety, and effectiveness are among the factors influencing the panel's decision on the premarket approval (PMA) application for the device, which is intended for implantation in the fallopian tubes for permanent female sterilization. Tubal occlusion devices that are placed laparoscopically have been previously developed and are supported by the published literature. Mr. Pollard said that the results of the CREST study highlighted by Ms. Costello should prove useful in putting the issue in perspective.
3. The device in question represents the next generation of devices for permanent sterilization. Although the new device is not supported by as much clinical experience as are other sterilization methods, it has been supported by the clinical trials conducted to date.
4. This PMA application, the result of the panel's deliberations, and its decision will serve as a model for the future review of new devices.

### **PRESENTATION FROM SPONSOR**

#### **Introduction**

**Cindy Domecus**

**Senior Vice President, Clinical Research and Regulatory Affairs**

**Conceptus, Inc.**

Ms. Domecus introduced the panel presentation team and acknowledged the FDA's input during the clinical research conducted on the Essure system. She informed the panel that Conceptus chose to develop Essure because of the need for additional contraceptive choices for women, as evidenced by the high rate of unintended pregnancies in the United States. The literature suggests that part of the reason for this high rate is due to patient dissatisfaction with reversible methods, which leads to imperfect use and unintended pregnancy. Current methods of permanent female sterilization, she said, require invasion of the abdominal cavity through surgery performed under general anesthesia, with its attendant risks.

Ms. Domecus went on to summarize the risks of tubal ligation via the transabdominal approach. Although these procedures are highly effective, they also carry significant risk. The great majority of complications with the transabdominal approach are related to incisions, blind insertion of instruments into the abdomen, and general anesthesia. In contrast, she noted that the transcervical approach avoids all three of these components.

### **Device Description, Mechanism of Action, and Placement Procedure**

**Jay Cooper, M.D.**

**Founder and Medical Director, Women's Health Research  
Clinical Assistant Professor, University of Arizona**

Dr. Cooper distributed samples of the Essure device to the panel members. He informed them that he has worked with Conceptus as an advisor through various iterations of development of the device and served as the Principal Investigator on the U.S. studies.

Dr. Cooper described the Essure microinsert as a soft, flexible, 4-cm device composed of an inner and an outer coil. Laced along the inner coil is a length of polyethylene terephthalate (PET) fibers. Placed in the uterotubal junction, the device can achieve a diameter of up to 2 mm. The leading edge of the device is ball tipped, which facilitates its placement into the proximal fallopian tube. The Essure device is radiopaque and can be seen to conform to the natural shape of the fallopian tube.

The delivery system consists of a handle with a rotatable thumbwheel and a guide wire that allows for one-handed deployment. Attached to the handle is an outer delivery catheter that is 1 mm in diameter and can be passed through the operating channel of a hysteroscope.

Dr. Cooper presented a series of photographs showing the delivery of the device and played an animation of the placement steps. He pointed out that the design of the delivery catheter aids the operator in deployment, as it is hydrophilic and becomes slippery and lubricated as it passes through the saline-filled uterine passage. Approximately 2 cm from the leading edge of the catheter is a black positioning bump that provides a visual aid to the operator in properly positioning the microinsert. Once this positioning bump can be seen to have reached the uterotubal junction, the release catheter is withdrawn and the device is free to expand to its natural diameter. The guide wire is then separated from the device, leaving it positioned at the uterotubal junction and spanning the diameter of the fallopian tube. The musculature of the uterus prevents the device from achieving its full diameter, thus accommodating to variable tubal widths and keeping it in place.

The mechanism of action of the Essure microinsert is expansion of the coils, which results in mechanical blockage, and tubal occlusion, which occurs through tissue ingrowth. Dr. Cooper said that the Essure procedure requires no or only minimal (5.5 mm) cervical dilatation and can be accomplished with the simplest of hysteroscopic procedures, similar to those used for diagnostic evaluations. The procedure is devoid of many of the risks and concerns of more advanced hysteroscopic procedures. Through saline distension of the uterus, the risk of intravasation is minimized, and no cutting or resection is required. Electrosurgery is not employed, the procedure is rapid, and intraoperative bleeding is uncommon.

### **Clinical Trials Summary**

#### **Cindy Domecus**

Ms. Domecus informed the panel that the Essure system underwent 2 years of clinical testing with earlier versions of the device before clinical testing of the “gamma” design began in 1998. Forty-six women were enrolled in the peri-hysterectomy study and 63 in the Pre-Hysterectomy Study, which yielded data on comfort as well as histological data to support the theorized mechanism of action of the device. Phase II trials of safety and effectiveness were conducted with 227 women who were candidates for sterilization. A pivotal trial of safety and effectiveness was conducted in 2000 in 518 women. Clinical testing of the device has involved a total of 854 women over 4 years.

### **Pre-Hysterectomy Study**

#### **Thomas Wright, M.D.**

#### **Study Histopathologist**

#### **Associate Professor of Pathology and Director, Division of Ob-Gyn Pathology**

#### **Columbia University**

Dr. Wright informed the panel that he is a paid consultant to Conceptus, Inc. and has no other financial interest in the company.

For the pre-hysterectomy study, the Essure microinsert was placed in awake women 1–30 weeks before scheduled hysterectomy. A total of 51 women wore the device for 1–30 weeks. Most of the participants had the device in place for 4–14 weeks.

Hysterosalpingography (HSG) was performed within 1 week of hysterectomy, and specialized histopathological tissue processing was carried out by a single histopathologist who was blinded to wearing time and clinical information. The embedded tube and device were cut into sections and ground down to allow examination of the relationship between the tissue, the fallopian tube, and the device. HSG results showed that 100% occlusion of the tubes occurred in all 51 women, including those wearing the device for less than 4 weeks.

Dr. Wright showed a photograph of a cross-section of the fallopian tube in a woman wearing the device for 4 weeks. He pointed out that even after this relatively short time, dense fibrosis could be seen to have formed between the inner and outer coils of the device, and the normal tissue architecture of the tube had been completely disrupted. In a cross-section from a woman

wearing the device for 13 weeks, the lumen appeared to be totally occluded by fibrosis. Smooth muscle cells could be seen to have migrated into the spaces between the inner and outer coils and among the PET fibers within the coils. Dr. Wright said that this event is typical of what is seen with PET devices used in other applications.

Histopathological features were graded in a blinded fashion. Over time, an increase in dense fibrosis and a reduction in acute inflammation was seen until a stable state of chronic inflammation and loose fibrosis was achieved.

Summarizing the conclusions of the study, Dr. Wright said that before hysterectomy, total tubal occlusion occurred in all participants at all time points, including those wearing the device for less than 4 weeks. The tissue response with the device was predictable and progressive, occlusive, and localized to the device, occurring within the normal tubal architecture 5 mm distal to the device and not extending to the serosa.

### **Pivotal Trial Results**

**Charles S. Carignan, M.D.**

**Vice President, Clinical Research and Medical Affairs**

**Conceptus, Inc.**

Dr. Carignan informed the panel that the objectives of the pivotal trial were to evaluate the safety of the placement procedure and participants' tolerance of and recovery from the procedure, the safety and participants' tolerance of the implanted microinserts, the occurrence of tubal occlusion at 3 months, and the effectiveness of the Essure device in preventing pregnancy, using a primary endpoint at 1 year. Women were followed at 1 week and 3 months after the Essure device was placed, during which time they relied on alternative forms of contraception. They were then evaluated after 3, 6, and 12 months of relying solely on the Essure device for pregnancy prevention.

The trial was conducted among 320 women in eight sites in the United States, 133 women in two sites in Australia, and 65 women in three sites in Europe. Adverse events occurred in only 3% of the women, and all of these events resolved before discharge. None of the women required major surgery, and the only hospitalization occurred in one woman who was observed overnight for a reaction to pain medication. Perforation occurred in only 1% of women, none of whom had any symptoms of perforation. Most women reported mild to no pain.

The average time to discharge after the procedure was 45 minutes. Fifty-eight percent of the women had no immediate post-procedure events. The most frequent events reported were cramping, pain, and nausea. Seventy-five percent of the women required no post-procedure analgesia, and 74% reported missing less than 1 day of work.

At 3 months after placement of the device, women underwent HSG to determine the location of the device and the extent of tubal occlusion. At this time they also received a pelvic examination and were asked questions about their comfort and satisfaction. Comfort was rated as excellent at all the study visits; only 3% of the women reported episodes of pain at more than one visit. Changes in menstrual function consisted of irregular menses, spotting or intermittent

intermenstrual bleeding, and changes in menstrual flow. Few of the women reported persistent changes in menstrual function. All changes in menstrual function were considered in light of the fact that 48% of the women had discontinued oral contraceptives.

Adverse events were defined as any untoward deviation from baseline. Women maintained daily diaries for 6 months. Multiple episodes of the same event were counted separately. The most common event rated as at least “possibly” related to the device was back pain, which occurred 43 times. Participant satisfaction with the device was high; from 3 months after placement and onward, more than 90% reported that they were “very satisfied” with the device.

No pregnancies were reported among any of the women relying on Essure in the pivotal trial. The current estimate of the 1-year effectiveness rate, based on the pivotal trial alone, is 100%, with a 95% confidence interval of 99.31–100%. No pregnancies were reported among the women in the Phase II trial. The combined 1-year effectiveness rate is also 100%, with a 95% confidence interval of 99.52–100%.

The conclusions drawn from the study, said Dr. Carignan, are that the Essure microinsert system is highly effective, yields high patient satisfaction with a well-tolerated placement procedure and a rapid return to work and normal activities, is comfortable and safe, and requires no general anesthesia or incisions.

## **Panel Discussion Questions**

### **Cindy Domecus**

Ms. Domecus addressed questions previously posed by the panel regarding the Essure system. (These questions appear in full in Attachment A.)

#### **Question 1: Effectiveness of Essure in comparison with other tubal sterilization methods:**

There were no reported pregnancies among women using the Essure microinsert during the first year of use. This rate is equal to or lower than that of other female tubal sterilization methods. As reported in Dr. Corignan’s presentation, the combined 1-year effectiveness rate was 100%, with a 95% confidence interval of 99.52–100%. The second-year effectiveness rate for the Essure device was also 100%, a rate equal to or lower than those for other sterilization methods.

**Question 2: Age characteristics in the Essure pivotal study in comparison with those in the CREST study:** The age range of women in the CREST study was 18–44 years. The pivotal study design was based on two age groups: under age 34 and over age 34. Regret was highest among the youngest age group; the age cap in the pivotal study was 40 rather than 44, as in the CREST study.

**Question 3: Mechanism of action/recanalization:** There is no evidence of long-term failure with Essure. Five women have relied on the system for 36 months with no reported pregnancies. The history of the use of PET fibers in cardiac valves, stents, and grafts has shown that they produce a durable dense fibrotic response. The device is designed to occlude a 1.2-mm section of the fallopian tube. Postmarket surveillance will be conducted to follow the women who participated in the Phase II study and the pivotal trial for 2 years.

**Question 4: Pelvic X-ray in lieu of HSG:** Ms. Domecus said that the plan to require pelvic X-ray instead of HSG to confirm the location of the microinsert is believed to be adequate because unsatisfactory locations could be detected on pelvic X-ray alone. The HSG patency rate with Essure is similar to that with incisional tubal sterilization published in the literature. Moreover, since follow-up HSG is not the standard of care for tubal ligation, the proposed plan to use X-ray is conservative.

**Question 5: Placement failure rate:** Eighty-three of evaluated failures to properly place the microinsert were attributed to proximal tubal occlusion that was not identifiable with the transabdominal approach. The placement procedure was shown in the pivotal trial to be well tolerated and was associated with minimal risks. High placement rates were achieved even in obese women and those with a history of prior abdominal or pelvic surgery. Ms. Domecus pointed out that these women are often the same ones who are refused laparoscopic surgery because of their increased risk for complications. She also observed that offering women a less invasive approach before a more invasive procedure is consistent with clinical practice in other areas of medicine.

**Question 6: Safety:** The panel's questions about safety were addressed by Dr. Corigan in his presentation.

**Question 7: Outline of training program:** The training program will consist of a full-day course with a didactic presentation and training manuals, followed by the use of a custom-designed placement simulator that allows for placement practice in rapid succession. Data will be collected on preceptored cases until formal sign-off from the training program. The participants will perform an average of five placements. A Technical Help Desk will be maintained for post-training assistance. The proposed training program is already in use in Canada, Europe, Australia, and Singapore.

Successful placement rates in commercial settings were found to be equivalent to those in the clinical trials, even though the average number of procedures per physician in commercial settings was less than half that in the clinical trials. For this reason, it is believed that the placement procedure will be generalizable to the commercial setting. Placement rates were not significantly changed with experience after the first five cases. Procedure duration decreases slightly with experience. Ease of use was most often rated by operators as "simple" or "moderately simple."

**Question 8: Postmarket surveillance:** Patients in the Phase II and pivotal trials will be followed for 5 years and will be requested to provide tissue samples and/or the microinserts from future extirpative surgery of the reproductive organs. Placement and adverse event data will be collected on all preceptored cases. Labeling of the device will carry a toll-free number for physicians to call in the case of adverse events and reportable events to the FDA.

## **Conclusion**

Ms. Domecus expressed the sponsor's belief that the data gathered in trials of the Essure microinsert represent "valid scientific evidence" in accordance with 21 CFR 860.7. She said that a reasonable assurance of safety and effectiveness has been established for the device, and adequate training and postmarket surveillance plans are in place to support the market release of the device. On the basis of the information and evidence presented, said Ms. Domecus, Conceptus respectfully requests approval of the Essure microinsert system.

## QUESTIONS FROM PANEL MEMBERS

In response to a question concerning the distribution of women according to race and ethnic background, the sponsor reported having obtained information for the pivotal but not the Phase II study. The distribution was as follows in the pivotal study: 5.4% black, 6.4% Latin, 0.4% Asian, and 0.4% American Indian for all study sites in the United States, Australia, and Europe. In the United States, the distribution was as follows: black, 8.8% average, range 2–25%; Latin, 10% average, range 2–32%; and Caucasian, 79% average, range 43–92%.

In response to a question about data on the mechanism of action of and biological response to PET fibers used in other medical devices, Dr. Wright said that PET fibers have a long history of use in cardiac grafts and other body sites. The response to PET fibers is well described in the literature: cells become attracted to the PET fibers, inducing an acute or chronic inflammatory infiltrate. Over time, the inflammatory process diminishes while the dense adhesive process increases. The literature on the use of PET fibers over a long period shows no long-term adverse effects. Neither are there any data implicating PET for producing neoplasms after many years of use (such as cardiac grafts placed in children).

Ashish Khera, Vice President, Research and Development, Conceptus, Inc., indicated that the materials chosen for the Essure device have a long history of use in medical applications. Ms. Domecus indicated that biocompatibility test results submitted in accordance with FDA guidelines in advance of conducting tests show that this material is not toxic or mutagenic in the chronic setting.

Dr. Cooper was asked about the decision to use prophylactic antibiotics before the placement procedure. He replied that this was left to the discretion of the investigators, only one of whom made routine use of prophylactic antibiotics.

In response to a question about what was done when perforation were noted, Dr. Cooper said that in those deemed to be candidates for traditional methods of sterilization, the devices were retrieved at laparoscopy. He said that in most cases the diagnosis of perforation was made at the time of placement. In a small number of cases, perforation was not noted until post-procedure X-ray. Retrieval in those cases was not problematic; the device was found lying in the omentum and could be easily removed. Dr. Carignan said that the longest time between perforation and retrieval was 4 years; in that case, the device was found in the pouch of Douglas and was removed. Among women whose devices were not retrieved, there were no reports of unusual pain that could be attributed to the location of the device.

Dr. Carignan said that a “fail-safe” mechanism consists of using the black positioning bump to properly locate the device. During training, he said, it is stressed that the position of the black bump must be maintained during the release of the device. A sudden loss of resistance should be recognized as a perforation and is an indication not to place the device.

Because the device spans the uterotubal junction, said Dr. Carignan, the method of removal is by cornual resection. Removal of a well-positioned device, however, is not recommended.

A question was asked about a requirement in the training plan for local versus general anesthesia in the five precepted placement procedures. Ms. Domecus said that this decision is left up to the physician.

Dr. Cooper was asked how many patients had preexisting pathology in the uterine cavity at the time of hysterectomy. He said that a low incidence of intracavitary pathology was found at the time of elective sterilization. Rarely did this pathology interfere with the ability to place the device. Asked whether he would place the device in the presence of a small amount of pathology, he answered in the affirmative.

A question was asked about the device’s labeling information, which contains little or no information about procedures done subsequent to placement of the device. Dr. Cooper was asked whether patients undergoing dilation and curettage (D&C) can still rely on the device or whether they are advised to use an alternative method of contraception. Dr. Cooper said that two of four women with luteal-phase pregnancies chose pregnancy termination via suction D&C. Despite the fact that they had not worn the device for the requisite 3 months at the time of D&C, these women relied on the device for long-term contraception afterward. There were five reports of women in the commercial population undergoing D&C without disruption of the device. It would be difficult to imagine, he said, that the suction created by the catheter in a D&C could dislodge the device, especially after 3 months of tissue ingrowth. Women with abnormal uterine bleeding, he said, should undergo a visual examination of the uterine cavity, which is good sense regardless of whether they have the device.

The reason for the recommendation against using electrocautery in women wearing the microinserts, said Dr. Cooper, is due to insufficient information on its effects. Physicians are warned not to use electrocautery within 4 cm of the device. In one case where the electrode touched the tip of a device, some blanching of the tube was seen.

Dr. Wright was asked how the microinsert creates adhesions in the fallopian tube but not in the uterine cavity. He said that in the tube, the outer coil of the device expands outward and causes localized trauma to the epithelium. This trauma stimulates an inflammatory response. Retrieved devices have shown some fibrosis immediately surrounding the inner coil containing the PET fibers. No dense adhesions or adipose tissue was seen in the tissue tied to the microinserts. Dr. Wright said that it is believed that the answer to the question lies in this cascade of events generated by the outer coil when the device is in place.

Although there is no experience in patients wearing the device who undergo in vitro fertilization (IVF), said Dr. Cooper, his personal opinion is that these patients will not have a problem with

this procedure. It is unlikely that the small area affected by the device, which is covered over with dense fibrosis, would interfere with pregnancy.

Dr. Cooper said that it is recommended that the device be removed if 15–18 coils are seen to be extending into the uterine cavity after placement. He said that the reason for this recommendation is that in these cases it has been shown that the device is likely to be expelled.

A question was raised as to whether ultrasound had been looked at as a way of confirming placement. Dr. Carignan said that in the Phase II studies, some investigators used ultrasound for this purpose but that this was not controlled for.

## **PRESENTATION FROM FDA**

### **Lisa Lawrence, R.N. Lead Reviewer, CDRH/ODE/DRARD**

Ms. Lawrence, lead reviewer for the Essure PMA, updated the panel on the status of the FDA review process for the device. She described the Essure device, highlighted the PMA review areas, and provided an overview of the IDE and PMA review history and the preclinical reviews.

In June 2001, FDA held a Determination/Agreement meeting with Conceptus, which sought an additional commitment from the agency as the pivotal study was underway. It was agreed that the FDA would file the PMA for the device, if there were at least 400 subjects in the pivotal study with 1-year follow-up, and at least 100 subjects in the Phase II study with 2 years of data. Bayesian statistics would be used to analyze the 1- and 2-year failure rates. The mechanism of action would be supported by histology data from 30 patients in the pre-hysterectomy study. Expedited review was requested on April 22, 2002, and granted on May 22, 2002, when it was determined that the device offers a significant advantage over existing approved alternatives. Preclinical reviews have been completed for animal studies and MRI compatibility studies. Reviews are ongoing for engineering, chemistry, and device sterilization of the material that will contact the patient. Appropriate testing was conducted on material safety. Inspections on bioresearch monitoring and manufacturing are also underway.

### **Julia Corrado, M.D. Medical Officer, CDRH/ODE/DRARD**

Dr. Corrado gave a historical overview of transcervical sterilization devices and reviewed the principle of operation of the device, its indications for use, and clinical studies on the Essure system.

Two investigational devices developed in the 1980s were completely unrelated to the Essure device and never saw any commercial use in the United States. Sterilization failures following the use of these devices were due to misreading of pelvic X-ray and/or HSG.

The clinical studies of Essure consisted of a peri-hysterectomy study to evaluate the feasibility of placement; a pre-hysterectomy study to evaluate placement, tolerance to inserts, and histology; and Phase II and pivotal studies for safety and contraceptive efficacy.

The objectives of the pre-hysterectomy study were to evaluate placement, tolerance to the placement procedure and relative long-term wear (14–20 weeks), stability of placement, and occlusion at 24 hours to 12 weeks and beyond. A total of 53 women wore the device from less than 4 weeks to more than 14 weeks; two were lost to follow-up. Tissue response to the device showed predominantly macrophages and lymphocytes, polymorphonuclear leukocytes at shorter wear times, and foreign-body-type giant cells at longer wear times. Dense fibrosis was present after 4 weeks. No serosal fibrosis or adhesions were seen, and the tubal architecture was normal 5 mm distal to the microinsert.

The Phase II study was conducted to determine the long-term safety of the procedure, the long-term stability of the microinserts, and the contraceptive effectiveness of the device. The study had a prospective, multi-center, nonrandomized design with a planned 5-year follow-up. Participants ranged in age from less than 28 to 45 years; the largest proportion of women were 34–45 years of age.

Eighteen women were treated with the beta device, a discontinued version for which placement rates were lower than for the gamma device. A total of 227 women were treated with the gamma device in a total of 233 procedures. At 3 months after placement, 97% of the women had bilateral occlusion of the fallopian tubes. Dr. Corrado noted that successful bilateral *placement* did not necessarily result in successful bilateral *occlusion*, although occlusion rates were high with successful placement.

No pregnancies occurred in 194 subjects at 12 months, and none occurred in 149 subjects at 24 months. The number of adverse events was small; there were six perforations and 153 instances of intraoperative pain out of the 233 procedures. Adverse events within 1 week of the procedure consisted of 188 reports of bleeding and fever that resolved within 12 hours in four subjects. One instance of expulsion occurred at 3 months post-procedure. Acceptability of the procedure was rated “good” to “excellent” by 90% of the subjects at 1 week, and 88–94% reported “excellent” tolerance at 3–24 months.

The pivotal study was a prospective, multi-center, nonrandomized, noncontrolled trial with a planned 5-year follow-up. The ages of the women in the study ranged from less than 28 to 40 years old; the largest proportion was 28–33 years. Of the 507 patients receiving the device, bilateral placement was achieved on the first attempt in 446. Bilateral placement was achieved in 18 women on the second attempt. Of these 464 patients, 452 are relying on Essure for contraception. No pregnancies had occurred at 12 months post-procedure in 408 of these women. Adverse events within 24 hours of the procedure consisted of one perforation, two cases of hypervolemia, and three cases of vasovagal response. Adverse events at 3 months were similarly small in number, consisting of four perforations and 14 expulsions. Intermenstrual bleeding occurred in 112 subjects, irregular menses in 49, heavier menses in 90, and lighter menses in 57. Only 12 patients had adverse events that prevented reliance on the Essure device.

Four luteal-phase pregnancies occurred before device placement and were not identified on the pregnancy test given before the procedure. Three of these women chose pregnancy termination and had no problems with the procedures.

Dr. Corrado noted that the device cannot be removed hysteroscopically. There were no requests for removal of the device among women in the pivotal study. Four attempts to retrieve the devices were made during alternative sterilization procedures performed after perforation was diagnosed on HSG at 3 months; two of these retrieval attempts were successful.

Patient comfort with the device was rated as “excellent” by 82% of women 3 months after placement and by 91% at 1 year after placement. Patient satisfaction was also high; 92% were “very satisfied” at 3 months and 95% at 1 year after the placement procedure.

Dr. Corrado noted that the clinical studies used HSG for placement confirmation, whereas Conceptus proposes the use of X-ray in lieu of HSG if device location is satisfactory. She asked the panel members for their input on this issue.

Dr. Corrado noted that the CREST study showed that the cumulative rate of sterilization failure continues to increase beyond 2 years. Ectopic pregnancies are more common in women with sterilization failure; the type of device and the age of the woman seem to have a bearing on the failure rate. She noted that the duration of follow-up in the CREST study makes it a landmark one; many women were followed out to 10 years. She said that this raises the question of how many women to follow and for how long.

**Gene Pennello, Ph.D.**  
**Division of Biostatistics, CDRH**

Dr. Pennello reviewed the study design of the Phase II and pivotal studies, described the patient population, presented a patient tree, and presented results of the effectiveness analysis and adverse events.

For the pivotal study, Bayesian statistics were used to analyze the first-year effectiveness rate. Phase II data were used as prior information. All five investigators in the Phase II study participated in the pivotal study as well. One pivotal study investigator who was not in the Phase II study participated in the peri- and pre-hysterectomy studies.

Protocol requirements in the pivotal study required participants to have had at least one live birth and to have four to eight coital acts per month. A total of 650 patients were initially enrolled in the pivotal study, of whom 518 eventually made up the intent-to-treat population. Bilateral placement was achieved in 464 women. Placement was successful after one attempt in 446 and after two attempts in 18 women. HSG was used to confirm satisfactory location. A total of 449 women were able to rely solely on the device for contraception.

Dr. Pennello described the use of Bayesian analysis as a scientifically valid way of combining previous information with current data. This method was used in the first-year effectiveness analysis, which includes all woman-months, including those from women followed for less than

1 year. Some women were censored from the study because of an insufficient number of coital acts for two consecutive cycles or because of reduced fertility of their partners.

In reference to Questions 1 and 2 from the panel, Dr. Pennello informed the panel that the Bayesian analysis combining data from the pivotal and Phase II studies did not adjust for the older ages in the Phase II study. Age adjustment is important, he noted, for labeling the device appropriately. He explained that the FDA approach to age adjustment is to adjust the first-year rate to the age distribution in either the pivotal or the CREST study, using the method of direct standardization. This method is commonly used in epidemiology to compare rates from multiple populations.

Dr. Pennello presented the sponsor's analysis of missing data. At the time of PMA submission, 27 women have been followed for less than 1 year post-alternate contraception. The Bayesian predictive probability of pregnancies is 98.90% for no pregnancies, 1.09% for one pregnancy, and 0.00% for two pregnancies.

Referring to Question 7 regarding the learning curve analysis for the placement procedure, Dr. Pennello presented hysteroscope times and first-attempt placement rates by procedure sequence for investigators with more than 20 procedures. The first five procedures required an average of 18.4 minutes hysteroscope time with placement rate ranged from 87.0%; for more than 20 procedures, the average time was 10.3 minutes, and the placement rate was 89.3%.

Notable results from the adverse events analysis included the observation that the rate of adverse events that initially prevented reliance on the device was significantly higher at one site (17%) than at other sites (0–3.5%). The expulsion rate also varied significantly by site, ranging from 0–13.5%. Seven women experienced sharp pain and three had sudden or severe cramping that was thought to be related to the placement of the device. There was a borderline association between unsuccessful bilateral placement and pain on average since the procedure. The rate of recurrent regular menses (5.9%) was 3.5 times that at baseline (1.7%), and the rate of recurrent intermenstrual bleeding (8.7%) was 3.8 times that at baseline (2.3%).

In summary, Dr. Pennello noted that the initial bilateral reliance rate was 92%, the first-year pregnancy rate was 0%, and patient satisfaction with the device was high. He acknowledged the issues of variation among sites in adverse events that prevented reliance and the effect of learning curve on hysteroscope time.

## **PANEL DISCUSSION**

The panel discussed Questions 1 through 8 (Attachment A) in light of the information presented by the morning's speakers.

### **Question 1: Effectiveness of Essure in comparison with other tubal sterilization methods:**

Questions were raised concerning the adequacy of the time period on which effectiveness data for the device were based, particularly in light of results from the CREST study showing that sterilization failure rates not only increase but seem to accelerate over time. Dr. Blanco pointed

out that the device will not be marketed as being more effective than other sterilization methods but will be presented to the consumer as having benefits and drawbacks, like other methods. Dr. Larntz noted that the number of pregnancies, zero, was as low as it could be, and that Bayesian analysis is highly appropriate for combining the data from the 2 clinical studies. Ms. Luckner suggested that the labeling for the patient should include the information that the device is called a “permanent” method based on only 1 year of data. It was agreed that this is a labeling issue and that the labeling can change as new information becomes available.

**Question 2: Age characteristics in the Essure pivotal study in comparison with those in the CREST study:** The panel discussed whether the data on effectiveness and safety are equally applicable to younger women, who will have the device in place for many more years than older women and who may be more fertile. The panel expressed concern that the procedure is not reversible, and patients must understand that the device should be regarded as a permanent contraceptive method. It was suggested that the labeling for the device include a statement for the physician about the importance of selection and counseling of patients.

**Question 3: Mechanism of action/recanalization:** The panel agreed that there is limited information on or understanding of the precise mechanism of action of the device. PET fibers have been used predominantly in vascular grafts, which are different from the fallopian tube. The members did not know of an analogous situation in which PET has been used to occlude an epithelium-lined structure. In regard to recanalization, it was observed that the purpose of the pre-hysterectomy study was to look at the device’s mechanism of action, not at how recanalization takes place. The panel agreed that the unique mechanism of action makes it less likely for recanalization to occur.

**Question 4: Pelvic X-ray in lieu of HSG:** Concern was raised over the possibility of doing the procedure differently in the commercial setting compared to the clinical studies. Of specific concern was the use of X-ray instead of HSG for device location and confirmation of tubal occlusion. The possibility of using ultrasound for this purpose was discussed. Dr. Blanco pointed out to the sponsor representatives that the occlusion results were high because HSG was used for confirmation of device location and tubal occlusion, but in the commercial setting pelvic X-ray will be recommended for this purpose instead. He said it may be unrealistic to expect the same results in the commercial setting when a different method is used.

Several panel members said that they would like to see data justifying the switch from HSG to flat plate X-ray for confirmation. This would require a group of women with the device in place to be checked at 3 months with pelvic X-ray. It was pointed out that because alternative contraception was not discontinued in women whose tubes were found to be patent, there is no way of knowing what the pregnancy rate might have been in those women if they had relied solely on the microinsert for contraception, especially since it is possible to confirm only device location, not tubal occlusion, with X-ray.

**Question 5: Placement failure rate:** Dr. Shirk asked how to manage patients in whom only unilateral placement can be achieved. Dr. Noller said that among gynecologists who perform only a small number of hysteroscopic procedures, the placement failure is likely to be higher than in the clinical studies. He also noted that gynecologists generally do not perform

hysteroscopy on awake patients, but rather use general anesthesia. He said that women need to be told about a contingency plan in which laparoscopy will be done if placement cannot be achieved via hysteroscopy.

Dr. Blanco pointed out that, to some extent, almost all studies of all devices are done by those with a particular interest in the procedure. He noted that the sponsor has presented an educational plan to train anyone who will be performing the placement procedure. This is a labeling issue, he suggested, in which appropriate counseling and notification of the patient must be done until more clinical experience can be gathered, at which time the labeling can be changed to reflect the data obtained from larger numbers. The panel agreed that direction to the physician should be built into the labeling concerning how to deal with failed and unilateral placement. Physicians should be told what to discuss with the patient in terms of what will happen if the device is determined to be properly positioned in only one tube.

**Question 6: Safety:** The panel discussed whether the safety profile is acceptable, particularly in terms of the risk of hypervolemia. Dr. Shirk said that saline infusion is fairly safe, especially since the procedure should be done with a small hysteroscope in the range of 5 mm and it is nearly impossible, even in 30 minutes, to infuse much more than 2–3 liters through an instrument of this size. The panel agreed that the labeling should emphasize a cutoff of 1,500 ml of infused saline to be used during the placement procedure.

**Question 7: Outline of training program:** The panel expressed the wish for more assurance from the sponsor as to the level of operator skill that will be achieved in the training program, particularly with regard to the operator's ability to perform the procedure using local rather than general anesthesia, which carries greater risks. Dr. Noller noted that the information in the patient inserts, as well as some of the comments made by the sponsor representatives, imply that the procedure will be done with local rather than general anesthesia. He said that it would be important to ensure in the training program that the procedure will be done with local anesthesia in the practice setting. The panel agreed that some hysteroscopic skill should be a requirement for this procedure.

Also discussed was the question of long-term follow-up and management, specifically with regard to the avoidance of electrocautery in patients wearing the microinserts. Given the mobility of the population, the burden is on the patient to ensure that subsequent physicians are informed of the presence of the device.

**Question 8: Postmarket surveillance:** The question was raised as to whether 5 years is an adequate length of time for postmarketing follow-up. Dr. Brown said that, given the data from the CREST study, she would like to see a longer time to determine whether the device will show the accelerated failure rate seen with other sterilization methods. To clarify this issue, Ms. Costello reviewed the slide from her presentation showing the cumulative probability of pregnancy after sterilization. She said that the rate of annual pregnancies in 4–10 years was the same as that in 1–3 years after sterilization, which is a cumulative and additive, not an accelerated, effect.

## **Additional Comments from Panel**

Dr. Blanco asked the panel members whether they had any further issues or questions to be mentioned or included. It was observed that it would be desirable to know what the failure rate of the device is in actual practice. Although women with the device will be followed, it was suggested that data be included on the placement failure rate in actual clinical practice. It was also suggested that a registry of users be maintained to track age and ethnicity and to collect failure rates as they occur.

The panel agreed that the issue of placement in younger women (e.g., mid-20s) needs to be addressed in regard to future desired pregnancies and the feasibility of IVF. It is important that nothing in the labeling implies that the procedure is anything other than permanent.

## **Simulator Demonstration**

The placement simulator that will be used in the training program was demonstrated to the panelists, with the view through the hysteroscope projected on a screen. The simulator includes different types of models of the uterus to simulate the different types that would be encountered in clinical practice.

## **OPEN PUBLIC HEARING**

### **Amy Pollack, M.D., M.P.H. President, Engender Health**

Dr. Pollack informed the panel that she is an obstetrician-gynecologist in the field of public health. Engender Health is a nonprofit organization that provides family planning and reproductive health services in the United States to women and men.

Dr. Pollack noted that clinical experience shows bilateral tubal sterilization to be safe and effective. About half of the 700,000 female sterilization procedures performed annually in the United States are interval laparoscopic procedures. About 250,000 women choose procedures that involve abdominal surgery with its attendant risks, which are not statistically related to the method of tubal occlusion but to the necessity of entering the abdominal cavity.

Female sterilization, said Dr. Pollack, is most often performed using local rather than general anesthesia, both in the United States and in other countries. In the United States, these procedures are done almost exclusively with short-acting agents because of the risks associated with general anesthesia. She emphasized to the panel the attendant risks of these procedures, despite which hundreds of thousands of women choose permanent sterilization. Dr. Pollack said that women choose permanent sterilization because they recognize the risks of temporary, reversible contraceptive methods. The side effects of these methods, she said, mandate the need for a transcervical option. She said that if there is a transcervical method of permanent sterilization that has been well tested, is shown to be highly effective and noninvasive, and does not require general anesthesia, then American women should have access to it.

In closing, Dr. Pollack said that, given the questions raised today, the developers of the device under consideration must be rigorous in their postmarketing surveillance. This option, she said, is one that is desperately needed particularly by low-income women living in areas of limited resources.

**Amy Allina**  
**Program Director, National Women's Health Network**

Ms. Allina informed the panel that the National Women's Health Network advocates for policies that promote women's health and evidence-based health care and practices. She suggested the following additions to the proposed patient information booklet to be distributed to patients using the Essure device:

- Information about how the effectiveness of the device may change over time and how the effectiveness of the device was tested, including the number of women and the number who became pregnant
- The statement that some women will not be able to have the device successfully placed and some of the conditions that may preclude placement, such as uterine polyps and endometriosis
- In the warnings section, greater detail on the unknown risks of uterine procedures using electrical energy
- Language about IVF and the reversibility of the procedure in accordance with the panel's prior discussion in this area
- That the effects on pregnancy and the fetus are unknown
- The statement that X-rays to confirm device placement and tubal occlusion may be preferable to HSG, but there is not enough information to determine this at present

In closing, Ms. Allina said that, in light of the need for expanded contraceptive choices and for increasing the safety of permanent sterilization, her organization supports the approval of the Essure system, which has the potential to advance women's health.

**Wayne Shields**  
**President and CEO, Association of Reproductive Health Professionals**

Mr. Shields told the panel that the Association of Reproductive Health Professionals (ARHP) represents about 2,400 health care providers who are directly involved in the practice of women's health and reproductive health. He said that ARHP places a strong emphasis on education, provider training, and patient counseling as the most important components of safe and effective contraceptive health care. ARHP supports the availability of as many safe and effective contraceptive options as possible and is pleased at the potential for the new option that Essure represents. Mr. Shields thanked the panel for the opportunity to comment and expressed his hope that the application would be favorably considered.

## **Additional Comments from Cindy Domecus**

Ms. Domecus thanked the panel for the opportunity to clarify a few points raised during their discussion.

First, in the matter of using HSG versus X-ray for confirmation of device location and tubal occlusion, Ms. Domecus said that X-ray would be recommended as a first step, with suspicious findings proceeding to HSG. All unsatisfactory locations of the device, she said, could be detected by X-ray alone. Concerning the determination of patency, she said that the tubal patency rate does not equal the pregnancy rate in tubal ligations, and that therefore failure of occlusion is not equivalent to failure of sterilization. She pointed out that with the Essure device, the tissue response was occlusive in nature and that changes in the tubal architecture was also seen.

Second, in the matter of training, Ms. Domecus informed the panel that five procedures is expected to be the average, not the minimum. Trainees will not be signed off until they have demonstrated competency in the placement technique. In regard to concerns about the generalizability of placement success, Ms. Domecus said that using an average of four procedures per physician, success rates are achieved that are very close to those in the trials. Among the placement failures evaluated by HSG, 83% were due to proximal tubal occlusion.

Third, the suggestion of tracking patients who wear the device has been considered, said Ms. Domecus. A card or ID to be carried by the patient is proposed in the PMA.

Fourth, concerning unilateral placement of a device, Ms. Domecus said that in the study protocol patients were allowed to return after HSG for another attempt at bilateral placement. Many patients opted to do this and were successful. The protocol, she said, will include this recommendation for unilateral placement at the first visit.

Fifth, Ms. Domecus told the panel that language about the safety and effectiveness of the device is present in the patient information brochure, as is the lack of data on reversibility. Language to this effect is included in the patient insert and the physician guide.

Finally, Ms. Domecus assured the panel that labeling information would be updated as soon as new data warranted a change, rather than waiting for 5 years until the end of the postmarket surveillance study.

## **PANEL DELIBERATIONS AND VOTE**

Dr. Blanco read aloud to the panel the options for premarket approval applications. A motion was made and seconded to approve the Essure device without conditions. The motion failed with one vote for, seven votes against, and one abstention.

Dr. Blanco asked for a motion to not approve the Essure device. No motion was made.

A motion was made and seconded for approval of the Essure device with the following conditions:

1. HSG for confirmation of device location and tubal occlusion will be required after placement of the device, as was performed in the original study. The FDA would be amenable to evaluating further data on alternative methodologies for correct device placement and tubal patency.
2. The training program for placement of the Essure device shall include knowledge of hysteroscopy as a prerequisite to performing the placement procedure.
3. Changes in the labeling shall include the following:
  - Clarified and more prominent information on the placement failure rate
  - Information about the correlation between patient age and changing her mind; emphasis in patient labeling about irreversibility of procedure
  - Warnings about metal allergy, electrocautery, and pregnancy occurring while the device is in place
  - The recommended maximum duration of the placement procedure and limit of 1,500 ml of saline
  - Clarification of the 99.8% success rate, including the numbers of patents
  - A recommendation that the placement procedure be performed during the proliferative phase
  - An example of educational written informed consent to provide to physicians
  - Recommendations on what patients should do in the event of a missed period; risk of ectopic pregnancy
  - Information on a contingency plan in the event that one or both devices cannot be satisfactorily placed
  - Training requirements as stated previously (item 2)
  - Continuation of observation of current patients for 5 years
  - Better assessment of failed insertion rates for patient counseling and labeling

The motion to approve the Essure system with these conditions was carried by a vote of eight in favor, none against, and one abstention.

## **ADJOURNMENT**

Dr. Blanco complimented the presenters on what he called the best presentation he had seen in 8 years of serving on the panel. He also commended the audience for their participation and comments and the FDA staff for their hard work.

The meeting was adjourned at 5:25 p.m.

## Attachment A: Discussion Questions

### Effectiveness

1. The results for the single-arm clinical trials featuring bilateral placement of the current (gamma) version of the Essure Micro-insert are provided below. How does the effectiveness of the Essure Micro-insert compare to other available methods for female tubal sterilization?

	number patients	number pregnancies	Bayesian estimate of pregnancy rate, 95% confidence interval <sup>1</sup>
Primary Endpoint: pregnancy at 1 year PAC (post-alternate contraception)			
Pivotal Trial	408	0 <sup>2</sup>	0% (0, 0.69%)
Phase II Trial	194	0	0% (0, 1.53%)
Combined	602	0	0% (0, 0.48%) <sup>3</sup>
Secondary Endpoint: pregnancy at 2 year PAC			
Phase II Trial <sup>4</sup>	149	0	0% (0, 1.65%)

<sup>1</sup> The Bayesian estimate given is the posterior mode (analogous to the maximum likelihood estimate in a non-Bayesian statistical analysis); confidence interval is Bayesian higher posterior density (HPD) interval (analogous to a 95% confidence interval in a non-Bayesian analysis)

<sup>2</sup> 4 luteal phase pregnancies

<sup>3</sup> does not adjust for the older age distribution in the Phase II study

<sup>4</sup> 1 pregnancy with discontinued (“beta”) version of device

2. The ages of the women in the pivotal study trial ranged from 21 to 40, with median age 32. The age distributions in the Pivotal Trial and in the CREST study (Peterson et al., *Am J Obstet Gynecol* 1996; 174:1161-70) are given below. Are these age characteristics appropriate for a study of this type?

Pivotal Trial	
age range	% of population
21-27	17%
28-33	47%
34-40	36%

CREST study	
age range	% of population
18-27	33%
28-33	35%
34-44	32%

3. The PMA presents results from a pre-hysterectomy 'proof of concept' study (n=52) where fallopian tube specimens were examined histologically 24 hours to 14-plus weeks following device placement.
  - a. What do the results of this study indicate about the mechanism of action of the Essure device?
  - b. Can results from this study shed any light on the likelihood of tubal recanalization in a long-term setting?
4. In the three months following device placement, the patient is instructed to stay on alternate contraception to allow for sufficient tissue in-growth to produce tubal occlusion.

In the Pivotal Study, an HSG confirming correct device placement and tubal occlusion was needed before the patient stopped alternate contraception. The Pivotal Study showed that the rate of bilateral occlusion was 96% of the number of correctly placed devices.

The Sponsor is proposing that in commercial use, alternate contraception can be stopped 3-months post-placement if a *pelvic x-ray* (i.e. not an HSG) confirms position of the device.

In view of the potential for placement to overrepresent occlusion, as well as the potential for incorrect interpretation of pelvic x-ray, is the sponsor's proposal adequate?

5. There was a 12% failure rate of bilateral placement on the first attempt.
  - a. Do the failure rates experienced by the investigators in this study provide an adequate indication of the failure rate that might occur when this device is in wider use?
  - b. Is this failure rate acceptable?

### Safety

6. The authors of the CREST study (Peterson et al., *Am J Obstet Gynecol* 1996; 174:1161-70) noted that sterilization "failure rates...should not be considered in isolation but rather in conjunction with safety and acceptability of the [female sterilization] procedures evaluated." The following are known risks of the Essure System placement:

- ?? Tubal perforation
- ?? Hypervolemia (due to high volumes of distention fluid over a short time)
- ?? Vaso-vagal response
- ?? Discomfort
- ?? Bleeding/spotting

Potential risks, not observed in the study, include sterilization failure, ectopic pregnancy and infection.

Given the advantages of the Essure System procedure (e.g. less anesthesia; avoidance of abdominal incision; patient satisfaction and comfort), is the safety profile of this device acceptable?

## Labeling & Training

7. For the pivotal study, the training program for investigators included:

- ?? Didactic materials
- ?? Practice on a hysteroscopic simulator
- ?? Device placement in peri-hysterectomy patients
- ?? Interpretation of device placement by hysteroscopy, HSG and pelvic x-ray
- ?? Proctoring of initial device placements in sterilization patients by experienced personnel

The sponsor is proposing to delete the requirement for placement in peri-hysterectomy patients, and to train investigators using a hysteroscopic model. The proposed Physician Training Program also includes proctoring of an unspecified number of "initial procedures" by a Conceptus-designated preceptor. Is this Training Program adequate?

## Post-approval Studies

8. An important finding from the longitudinal CREST study (Peterson et al., *Am J Obstet Gynecol* 1996; 174:1161-70) was that the risk of sterilization failure persists for years after the procedure (and varies by method of tubal occlusion and patient age).

At present, only one- and two-year contraceptive efficacy data are available for the Essure System. Conceptus does plan to follow all Phase II and Pivotal Study subjects out to five years post-device placement.

Is five-years an adequate time-frame for post-marketing follow-up for this device? Does the panel have recommendations about how to minimize loss-to-follow-up? Are other elements of a post-approval study needed?

I certify that I attended the Open Session of the Obstetrics and Gynecology Devices Advisory Panel Meeting on July 22, 2002, and that this summary accurately reflects what transpired.

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Joyce Whang, Ph.D.  
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Jorge D. Blanco, M.D.  
Panel Chair

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