SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Contraceptive Tubal Occlusion Device and Delivery System

Device Trade Name: Adiana Permanent Contraception System

Applicant's Name and Address: Hologic, Inc.
250 Campus Drive
Marlborough, MA 01752

Date of Panel Recommendation: December 13, 2007

Premarket Approval Application (PMA) Number: P070022

Date of FDA Notice of Approval: July 6, 2009

Expedited: Not Applicable

II. INDICATION FOR USE

The Adiana Permanent Contraception System is indicated for women who desire permanent birth control (female sterilization) by occlusion of the fallopian tubes.

III. CONTRAINDICATIONS

The Adiana Permanent Contraception System should not be used in a patient who:

- is uncertain about her desire to end fertility
- has clinical evidence of an active pelvic infection or history of a recent pelvic infection
- has intra-uterine pathology which would prevent access to either tubal ostium or the intramural portion of either fallopian tube (such as large submucous fibroids, uterine adhesions, apparent uni- or bi-lateral proximal tubal occlusion, suspected unicornuate uterus, etc.)
- is pregnant or suspects pregnancy
- is currently less than three months since her last pregnancy
- has previously undergone a tubal ligation
- is currently taking immunosuppressive medications (e.g., steroids)
- has a known allergy to contrast media

IV. WARNINGS AND PRECAUTIONS

A list of warnings and precautions can be found in the Adiana Permanent Contraception System labeling.

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V. DEVICE DESCRIPTION

The Adiana Permanent Contraception System consists of three principal components:

- Silicone Matrix (two matrices, one per tube);
- Hysteroscopic Delivery Catheter; and
- Radio Frequency (RF) Generator to deliver thermal dose to tube prior to implantation.

Principle of Operation

The Adiana Permanent Contraception System is used to place a silicone implant, called a matrix, into each fallopian tube of the female patient to effect tubal occlusion and permanent sterilization. The delivery catheter is introduced into the patient through the operating channel of a hysteroscope, transvaginally and transcervically. The physician will require a separate delivery catheter to place individual matrices in each of the two fallopian tubes. (Two delivery catheters are needed per patient since each delivery catheter contains a single matrix.) A black mark on the catheter, proximal to the electrode array and matrix, is visualized to confirm correct catheter placement prior to silicone matrix delivery. Device position is confirmed by the RF Generator via the position detection array on the tip of the catheter.

Once placement inside the intramural section of the fallopian tube is confirmed, the distal tip of the catheter delivers RF energy to the electrode array. Thermocouples in the catheter tip are used to maintain a constant temperature of 64°C for 60 seconds (maximum of 120 seconds of treatment per tube during a single procedure in the event that a procedure is terminated due to loss of adequate tissue contact). This creates a lesion within the fallopian tube (including destruction of the endosalpinx).

After the thermal dose is delivered, the release mechanism in the catheter is then actuated to deploy the matrix in the region of the tube where the lesion was formed. The endothelial damage provided by the RF energy encourages a tissue ingrowth response (i.e., wound-healing response). The implanted matrices provide attachment sites for tissue ingrowth, which secures the matrices in place by filling the voids in the implant. The physician conducts a hysterosalpingogram (HSG) three months after matrix placement to confirm contraceptive tubal blockage. Thus, the Adiana procedure can be described as the following four step procedure:

- Step 1: delivery (via hysteroscopy) of catheter to the fallopian tube and bipolar radiofrequency energy to create a superficial lesion in the fallopian tube

- Step 2: deployment of the implantable matrix in the area of the superficial lesion

- Step 3: use of a reliable form of contraception until tubal occlusion is confirmed 3 months following device placement

- Step 4: confirmation of bilateral tubal occlusion by an HSG; begin reliance on Adiana Permanent Contraception

Matrix

The non-absorbable matrix consists of a fully cured silicone elastomer formed into a unique three-dimensional architecture that is designed to provide a permanent scaffold which allows for "space-filling" and occlusive tissue in-growth. The matrix is cylindrical in shape with a diameter of 1.6 mm and length of 3.5 mm. The matrix is packaged within the electrode sheath, which compresses the matrix (maximum 0.2 mm). When the matrix is released, it expands approximately to its original shape and volume within the fallopian tube.

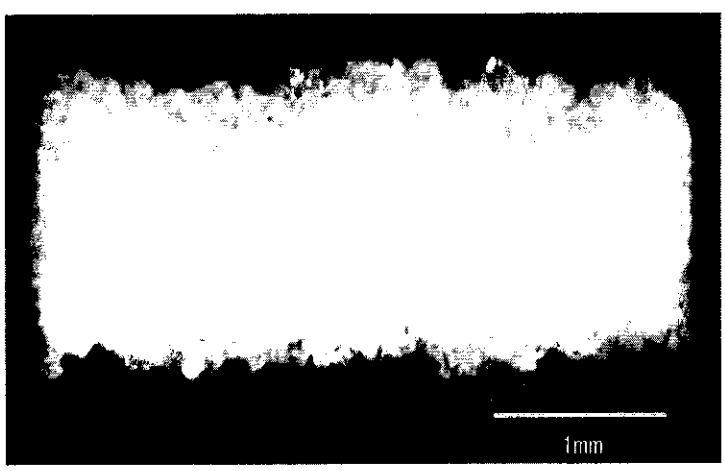

Figure 1a: Entire matrix, side view

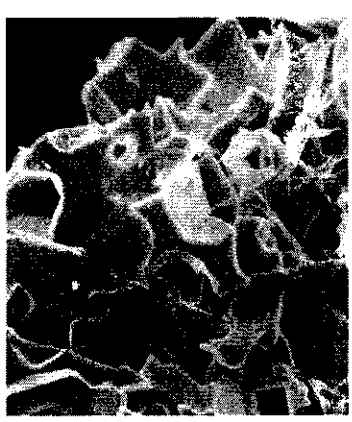

Figure 1b: Close-up view of matrix showing random architecture of pores

Delivery Catheter

Each delivery catheter contains one pre-loaded matrix, and it is introduced hysteroscopically into the fallopian tube where the matrix is deployed. The delivery catheter includes an electrode sheath configuration at its distal end. The electrode array consists of four stainless steel bands placed along the distal tip of the catheter. The bipolar electrodes enable heating of the surrounding tissue.

The delivery catheter and handle is 58 cm in length. It attaches to a connector cable that is 49 cm in length. The maximum outer diameter of the shaft is 0.065 in. (1.65 mm). The distal tip has a maximum outer diameter of 0.053 in. (1.34 mm). The catheters are supplied sterile, for single-use only. They are placed in a tray with a Tyvek lid.

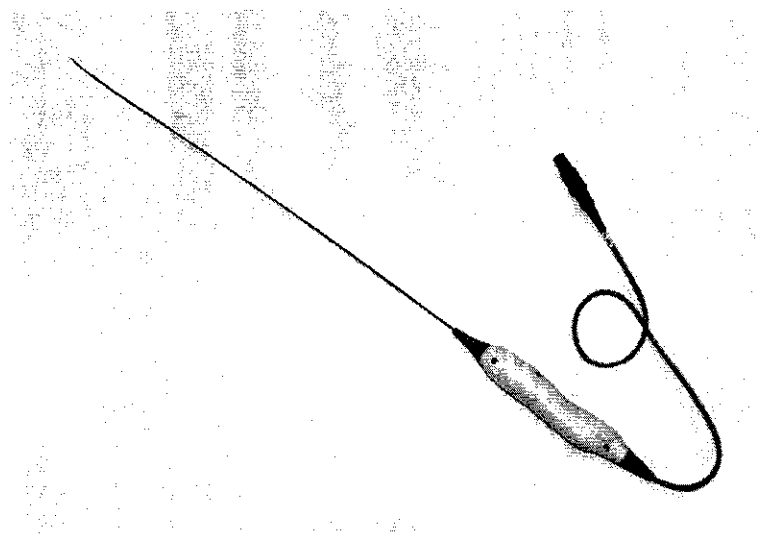

Figure 2: Adiana Delivery Catheter

The delivery catheter consists of three principal components:

- handle and cable;
- shaft; and
- distal tip (electrode sheath).

Handle and Cable

The handle consists of two polycarbonate plastic shells attached together with mechanical fasteners. Contained within the handle shells are conductor wires, electrical connections, the matrix release mechanism, and a cable strain relief. Conductor wires within the catheter sheath/shaft connect the electrode bands and thermocouples on the catheter's electrode sheath with a connector block that is located in the handle. An 18-inch pigtail extension cable, for use in connecting the sterile delivery catheter to the non-sterile extension cable from the RF generator, is also connected to this connector block via conductor wires. All

connections on the smart block are potted to ensure electrical isolation and mechanical stability.

The matrix release mechanism consists of a pre-loaded spring and a fluid filled dampener that are assembled into a sliding mechanism. The slide mechanism includes a latch that prevents any motion until activated by the user. Depressing the button releases the latch, allowing the sliding hub to retract under the force of the spring/dampener.

Shaft

The delivery catheter outer shaft is made of polyimide tubing with a polytetrafluoroethylene (PTFE) lining. The outside shaft covers the conductor wires, matrix release mechanism and thermocouple wire and insulates them from other equipment and from the patient.

Distal Tip (Electrode Sheath)

The electrode sheath assembly is located at the distal end of the delivery catheter shaft and is mechanically connected to the handle retraction mechanism. It is constructed from polyurethane plastic with a PTFE liner. It contains the atraumatic tip, the silicone matrix, the position detection array (PDA), the RF electrode array, and a black polyurethane plastic band (black visual position mark) located at the proximal end of the PDA (approximately 1.4 cm from the tip). A matrix exit hole is located on one side of the sheath approximately 3 mm proximal to the end of the distal tip.

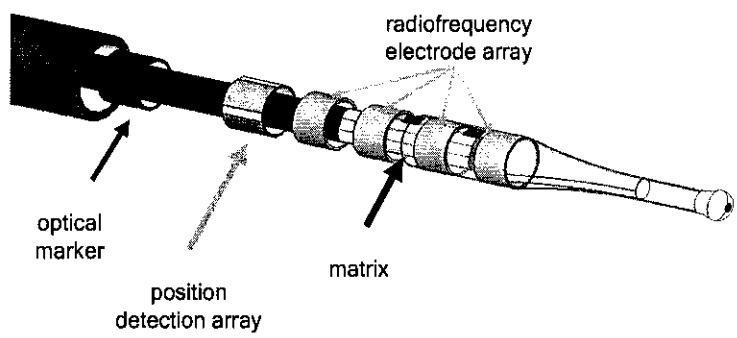

Figure 3: Delivery Catheter (Distal Tip)

The bipolar electrode sheath assembly is 6.0 ± 0.5 mm in length and is comprised of four stainless steel band electrodes, each 0.047 inches in diameter, and two thermocouples. The delivery catheter electrodes and thermocouples are arranged on the sheath, one thermocouple is located between 2nd and 3rd bands and the other is between the 1st and 2nd bands. The proximal thermocouple is used as a

control signal to regulate the RF generator output level. The distal thermocouple is used to monitor distal tip temperature as a safeguard for RF generator control.

The PDA is located on the electrode sheath 1 mm proximal to the electrodes. The PDA is a circuit which includes sensors attached circumferentially and equidistant from each other on the tubing (at 3, 6, 9 and 12 o'clock positions). The circuit senses circumferential tissue contact by the delivery of a small current from the RF generator through the PDA circuitry. When all four sensors are in tissue contact, the RF generator detects the electrical impedance created by the current traveling through the tissue. When a preset threshold for the impedance is reached, the display indicates proper contact. The RF generator will not allow the delivery of RF energy until the PDA circuit signals that all four sensors are in tissue contact.

A full catheter length push rod assembly, made from a stainless steel hypotube, polyurethane plastic and a nitinol core wire with a micro spring tip, is located within the electrode sheath and catheter shaft. The proximal end of the push rod is attached to the chassis of the slide assembly in the proximal handle. The distal end of the push rod is located within the internal diameter of the electrode sheath and against the proximal end of the matrix. Upon depressing the matrix delivery button on the delivery catheter handle, the electrode sheath retracts while the push rod assembly remains static leaving the matrix in the tubal lumen.

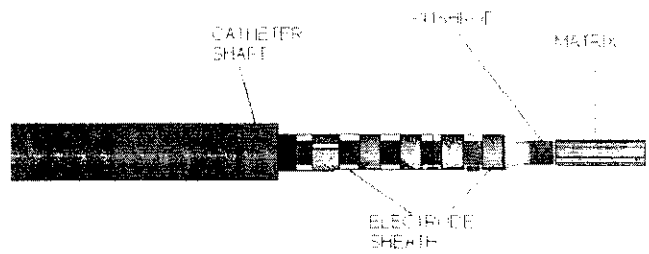

Figure 4: The electrode sheath has been retracted over the push rod into the end of the catheter shaft, exposing the matrix which exits the catheter tip.

A lubricious coating is applied to the external portion of the sheath material distal to the most proximal electrode band. This coating has been added to aid in tubal placement.

Radio Frequency Generator

The RF generator is designed to deliver low level RF energy (<3 Watts) to treat the intramural portion of the fallopian tube prior to matrix placement. Energy is delivered to four band electrodes located on the delivery catheter. This electrode array emits electrical energy that creates a thermal lesion adjacent to where the

matrix is to be placed. Output from the RF generator is automatically regulated to maintain a desired tissue temperature during lesion formation. To control cell destruction and reduce risks of unintentional damage to other organs, a feedback system adjusts output current in response to tissue temperature via a thermocouple between the two middle band electrodes.

The RF generator is a microprocessor-controlled, bipolar electrosurgical generator with automatic temperature control and a unique tissue contact sensor. The RF generator has a liquid crystal display front panel that prompts the operator through the sequence of steps to complete a procedure. During use, the RF generator monitors catheter outputs and signals to determine proper device placement, to control lesion creation, to ensure matrix delivery, and to detect error conditions. Treatment parameters of the RF generator are controlled at 64°C for 60 seconds using a temperature controlled feedback system. All treatment parameters are automatically controlled. There are no user-selectable settings for power, energy, or time.

The RF generator is approximately 14 in. W x 18 in. D x 4.25 in. H and weighs approximately 15 pounds. It includes a foot switch for control of certain generator functions and a cable to connect the generator to the delivery catheter.

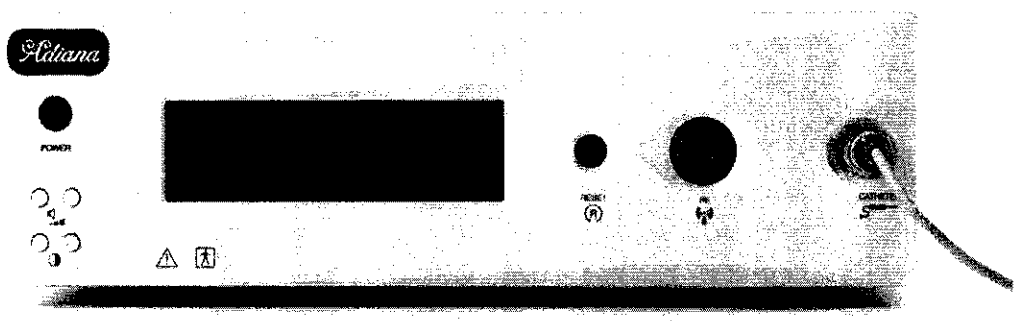

Figure 5: RF Generator

See the Operator's Manual for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The following alternative practices or procedures are currently available for permanent female sterilization:

- Hysterectomy

- Salpingectomy
- Tubal ligation
- Tubal coagulation (bipolar and unipolar methods)
- Tubal application of clips or Silastic® rings
- Tubal sterilization implant (metallic).

VII. MARKETING HISTORY

Hologic received CE marking approval for the European Union for the Adiana Permanent Contraception System in January 2009. The device has not been withdrawn from marketing for any reason related to its safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g. complications) associated with the use of the device.

- Ectopic Pregnancy
- Hyponatremia (associated with uterine distention)
- Cramping
- Vaginal Spotting
- Post-procedure Bleeding
- Pelvic Pain
- Back Pain
- Nausea
- Headache
- Vomiting
- Post-procedural Pain

The following adverse events were not experienced by women who participated in the clinical trial to evaluate the Adiana System but are still possible:

- perforation of the uterus or fallopian tube;
- perforation of internal bodily structures other than the uterus and fallopian tube;
- adnexal infection/salpingitis;
- adverse events associated with hysterosalpingogram (HSG);
- the effect of future medical procedures that involve the uterus or fallopian tubes on the ability of the Adiana matrices to provide protection against pregnancy;
- adverse events associated with surgery attempting to reverse the Adiana procedure, as well as adverse events associated with pregnancy following a reversal procedure or an *in vitro* fertilization (IVF) procedure; and

- adverse events associated with gynecological surgical procedures (e.g. endometrial ablation).

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

***In Vitro* Testing**

Developmental testing of the Adiana Permanent Contraception System was conducted using uteri that were obtained following elective hysterectomy. The objectives of the feasibility testing were as follows:

1) to evaluate the safety of using RF energy for destruction of the endosalpinx at the utero-tubal junction (intramural portion of the fallopian tube);
2) to evaluate the tissue response to various levels of RF energy; and
3) to evaluate different delivery catheter and electrode configurations.

Based upon these tests, the following were concluded:

- A catheter with a 6-mm long, four electrode bipolar array created the most uniform lesions.
- Treatment with the delivery catheter's electrode array at 64°C for 60 seconds is safe in that the lesion created is shallow, does not extend to the serosal surface, and causes no significant serosal temperature rises (max 3.6°C).
- Data from the Phase I preclinical in vitro trial reports that treatment at 64°C for 60 seconds yields a high degree of tissue ablation (78.5%), a lesion length of 5.14 mm, and a lesion depth of 0.385 mm. The lesions created were uniform and reproducible.
- Meta-analysis on all *in vitro* results where the 64°C for 60 seconds treatment cycle was used, showed an average 93% epithelial ablation rate with a range of ablation from 35 to 100%. The average lesion depth was 0.514 ± 0.097 mm.
- The use of a lubricious coating on the delivery catheter does not impact lesion formation.
- Application of RF energy to the same position twice does not result in an adverse rise in serosal temperatures, and the size and depth of resulting lesions were not adversely impacted.
- The Adiana RFG (Software Revision B) and the Radionics RFG had similar results in relation to lesion depth, lesion length and percent epithelial ablation.

Mechanical Testing

A battery of mechanical tests was conducted on both the matrix and the delivery catheter. These studies were performed on samples of final, finished, sterilized devices to verify that the design output conforms to the design input requirements described in the product specification.

Testing of the implantable matrix included the following:

Test	Specification
Visual inspection	The porous surface must be uniform, without unusual voids, cracks, seams, or patches of smoothness
Dimensional inspection	Maximum average OD: ≤ 1.80 mm Minimum average OD: ≥ 1.40 mm Matrix length: 3.50±0.25 mm
Tensile strength	Tensile values of cycled* and non-cycled groups will not be significantly different (~ 0.31 lbs.)

*Cycling involved repetitive (~ 90,000) compression (0.1 – 0.4 mm) of the matrix

Testing of the delivery catheter included the following tests:

Test	Specification
Visual inspection	The length of the shaft should be smooth and have no cuts or other defects
Dimensional inspection	Catheter working length: 40.5±0.5 cm Sheath length: 24.0±2.0 mm Sheath mark position: 14.5±1.0 mm Shaft OD: 0.060±0.005"
Connectivity/Insulation	Proper connectivity to each PDA wire, electrode band, and the matrix ejection loop wire
Hysteroscope insertion and removal	No permanent kinking will be present when the device has completed the insertions and removals
Compressive Loading	Maximum compressive load ≤ 0.44 lbs.
Device Rotation	The catheter handle/shaft assembly will withstand the full rotation
Fluid exposure/shaft leak test	Fluid leakage ≤ 28.4 g in 10 minutes
Lesion formation/release actuator	The catheter will withstand 60 seconds of RF cycle with no error. The release activation mechanism will operate with ≤ 6.0 lbs. force.
Electrode tensile	Tensile force: ≥ 0.55 lbs.

Rotational turns to failure	≥ 4
Electrode sheath/polyimide junction tensile	Tensile force ≥ 1.0 lbs.
Proximal sheath ring bond	Tensile force ≥ 5.0 lbs.
Catheter shaft to strain relief	Tensile force ≥ 3.0 lbs.
Push rod crimp joint	Tensile force ≥ 5.0 lbs.
Push rod to chassis tensile	Tensile force ≥ 5.0 lbs.

Note: The table includes a partial list of the specifications.

The results verify that the design output conforms to the design input requirements described in the product specification.

Electrical Safety/EMC Testing

The following tests were conducted on the delivery catheter:

- dielectric withstand (cable and pigtail);
- high frequency leakage current (cable and pigtail); and
- dielectric withstand of accessory handles.

The devices passed all tests and all data was within acceptance criteria.

The RF generator was tested to:

- IEC 60601-1:1998+A1+A2 (general requirements for safety);
- IEC 60601-1-2:2001+A1 (Electromagnetic Compatibility);
- IEC 60601-1-4:1996+A1 (Programmable Electrical Medical Systems); and
- IEC 60601-2-2:1998 (applies to High Frequency Surgical Equipment)

Device testing included the following:

Test	Specification
AC mains configuration test	DC voltages: 12Vdc±10%, -12Vdc±10%, 5Vdc±10%
Indicators and audible beep	Audible tone between 65 and 85 db at 1 meter away
RF waveform test	RF frequency in the range of 460.8 kHz±1%
Output voltage and current range test	Delivers 3W±5%±0.2W into a 100 Ω resistive load
RF measurement accuracy	The unit under test shall measure power to within an accuracy of ±5%±0.2W
Temperature measurement accuracy	The system shall measure temperature to within an accuracy of ±1.5°C over the range 50°C to 90°C
PDA measurement	PDA measurement shall be within ±10%±25Ω over the range 2000Ω-3000Ω

High frequency leakage test	HF leakage current from either pole of the bipolar output to earth through a 200 ohm non-inductive resistor to shall not exceed 3.16 V (RMS)
Defribillator-proof test	No damage to unit after applying 2kV discharge
Clock accuracy	Less than 3.9 second error over 24 hours
EMC test	Meets EN55011 in standby mode
Temperature measurement range	Thermocouple readings at the 20°C setting are with the range 17-23°C
Clock battery life	Estimated clock battery life is at least 10 years
PDA operation during RF output	Measurements are within the ±10%±25 ohm specification
Power to catheter ID resistor	Maximum power to the catheter ID resistor ≤ 1/8 Watt
Operation at 50 Hz line frequency	System completes the 60 second simulated ablation without error (at 200 V, 220 V, 230 V, and 240 V settings)

Note: The table includes a partial list of the specifications.

The device passed all tests. The hardware validation and verification testing is thorough and appropriate.

Software Testing

Software controls both the RF output based on thermocouple temperature feedback and the 60 second length of treatment. A menu driven display guides the operator through the entire procedure. The applicant stated that there were no user-selectable settings for power, energy or time, in that all treatment parameters are automatically controlled.

The applicant provided acceptable documentation demonstrating that they have developed the software for this device under an appropriate software development program; that they have performed a software hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provided the foundation for assuring, to the extent possible, that the software would operate in a manner described in the specifications, and in no other way. Tests included the following:

- Power On Self-Tests
- Standby State "Connect Catheter Mode"
- Ready State "Access Tube Mode"
- On State "Complete RF Mode"
- Done State "Place Matrix Mode"
- Error State "Detection of any recoverable error"
- Fault State "Detection of any unrecoverable error"

All tests were successfully passed.

Thermal Testing

The applicant developed a computer model (COSMOL Finite Element Method) of the heat distribution from the four electrode bands on the RF catheter. This computer model predicted a lesion size of 6.8 mm long and 1.3 mm deep at the electrode midpoint. The changes in the following parameters were found to have little effect on the lesion size: electrical and thermal conductivity, blood perfusion rate, and inter-electrode spacing. The Adiana system has all electrode and thermocouple wires situated on the proximal side of the catheter. The computer simulation provided by the applicant assumed the effect of these wires in potentially generating asymmetric heating is negligible. It is unlikely that the wires cause any significant asymmetrical heating.

Biocompatibility

The applicant conducted biocompatibility testing on the matrix based on test requirements for a permanent implant. The delivery catheter was tested based on requirements for a device with limited (less than 24 hour) direct contact with mucosal tissue and the split introducer was tested based on requirements for a device with limited indirect contact with mucosal tissue.

Component	Body Contact	Contact Duration	Biologic Tests Conducted
Delivery Catheter	Surface Device with Tissue Contact	A- Limited (<24 hrs)	1. Cytotoxicity 2. Sensitization 3. Irritation 4. System Toxicity
Split Introducer	Surface Device with Tissue Contact	A- Limited (<24 hrs)	1. Cytotoxicity 2. Sensitization 3. Irritation 4. System Toxicity
Matrix	Implant Device with Tissue Contact	C – Permanent (>30 days)	1. Cytotoxicity 2. Sensitization 3. Intracutaneous Reactivity 4. Pyrogenicity 5. Hemolysis 6. Genotoxicity 7. Implantation 8. Carcinogenicity 9. System Toxicity 10. Reproductive Toxicity

Table 1: Biocompatibility Testing

Biocompatibility studies conducted to support the safety of the Adiana Permanent Contraception System were assessed against the requirements of International Organization for Standardization (ISO) 10993-1: 2003, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing.

The test results indicated the silicone matrix did not cause cell lysis, sensitization, significant irritation, systemic toxicity, genotoxicity, or toxic effects on muscle. The delivery catheter and split introducer passed cytotoxicity, irritation, sensitization, and systemic toxicity testing. Biocompatibility test data supplied for the matrix, delivery catheter, and the split introducer were acceptable and complete.

Sterilization

The delivery catheter is a sterile single-use disposable, not intended for reuse or re-sterilization. The delivery catheter pre-loaded with the matrix, as well as accessories, are packaged in a single tray and are sterilized by steam (moist heat). The moist heat sterilization validation process involved use of the "Overkill" cycle method per ANSI/AAMI/ISO 11134-1993, which confirmed a Sterility Assurance Level of 10^{-6} for the selected biological indicator, *Bacillus stearothermophilus* (*Geobacillus stearothermophilus).*

For sterilization revalidation, the applicant utilized process challenge devices that were comparable to the Adiana delivery device in resistance to sterilization. Revalidation is to be conducted at least annually. Bioburden was evaluated approximately quarterly by the applicant to demonstrate ongoing control of the manufacturing environment. The sterilization data supplied for this delivery catheter and matrix was acceptable and complete.

B. Animal Studies

The applicant employed two different general protocols in the development of the Adiana System.

- Short term – evaluate ingrowth, tubal occlusion, and RF lesion creation
- Long term – evaluate pregnancy prevention and conduct histological analyses

The rabbit fallopian tube was used as the model for assessment of acute RF performance, tissue ingrowth into the silicone matrix, fallopian tube occlusion, and pregnancy prevention.

Short Term

The applicant conducted short term tubal implant studies in rabbits to evaluate the following:

- Matrix material, design, and construction
- RF electrode configuration
- Catheter coating effects
- Sterilization method effects
- Production validation tests

The applicant also conducted another short-term study to assess the ability of matrices that had been aged for one year inside the catheter to expand and support tubal occlusion in rabbits as compared to uncompressed matrices. Results of the dye test for the short-term study showed that none of the tubes in either group were patent following explant, and that no statistical differences between the parameters assessed in each group were observed. However, wide variation within groups for individual parameters was reported to make detecting group differences more difficult. It was also noted that the remaining epithelium layer present was greater in the aged group. This event was reported to be more a function of the RF treatment procedure in these animals and likely not related to the matrix. From this data, the applicant concluded that matrices stored compressed in the delivery catheter for one year gave similar ingrowth responses and showed similar responses when subjected to dye testing.

Long Term

The applicant conducted two longer-term animal studies (rabbit), lasting 12 months, evaluated the ability to occlude fallopian tubes and prevent pregnancy. These longer term studies also included histological analyses and tubal patency testing as well as breeding tests to assess the ability to prevent pregnancy. Results of the longer-term studies showed that pregnancy was prevented in all rabbits treated with the Adiana System. Following explant of reproductive tissues, the retention rate of matrices was shown to be > 95%, and that all tubes containing a matrix were shown to be occluded using a dye pressure test.

Histological assessment of the tissue samples from rabbits demonstrated that all groups showed space filling tissue ingrowth that was sufficient to cause tubal occlusion, despite differences in ingrowth scores due to variations in the percentage of remaining epithelium, and presence of closed vascular structures, inflammatory cells, giant cells, fibrosis, and necrosis. The host cellular ingrowth was characterized to include a combination of different cell types: fibroblasts, macrophages, giant cells, inflammatory cells, epithelial cells, and extracellular matrix.

The Adiana procedure can be considered to be effective when the matrices are appropriately placed within the lumen of the oviducts and the procedure appeared to be effective in rabbits following implantation for one year.

C. Additional Studies

Packaging

As stated before, the Adiana Permanent Contraception System is comprised of the delivery catheter (with implantable matrix) and the RF generator packaged separately.

The delivery catheter is for single-use and is not intended for reuse or re-sterilization by the user. Each catheter is packaged in a single tray along with an Accessory Introducer in packaging that is compatible with steam sterilization. The packaging consists of a polycarbonate thermoformable tray and a Tyvek® lid. The device components are sterilized and packaged in a controlled environment.

Maintenance of sterile package integrity was confirmed by whole package integrity testing as demonstrated by visual inspection, Burst Testing of package seals (ASTM F 2054-00), Gross Leak Detection in porous package material (Bubble test) ASTM F2096-04, and Detection of Leaks in Heat Seal (SPMC 005-96). Results from these four tests verified the thermoformed tray packaging system for the Adiana delivery system was capable of maintaining package integrity, following simulated conditions of distribution and handling. The RF generator is a non-sterile, reusable component. Following exposure to simulated conditions of distribution and handling, packaging test results verified that the packaging system for the RF generator is capable of maintaining product function and package integrity.

Shelf-Life Testing

The applicant conducted shelf-life testing of the disposable catheter/matrix assembly on product that was aged under real time aged and accelerated conditions (ASTM F1980). Testing addressed functional performance and the sterile barrier (ASTM F88-07-Seal Strength Testing). To achieve accelerated aging, package systems were sealed inside an aging chamber and subjected to a temperature of 70° C with relative humidity uncontrolled for 16.13 days. The product and packaging were shown to maintain their material stability, product functionality, labeling, and package integrity over time. These studies were used to establish a one-year shelf life.

The following was noted during real time testing of the matrix. Matrices stored ("aged") in the delivery catheter for 1 year are compressed throughout that time period, and – upon deployment – the matrices do not immediately expand to their original outer diameter design specification of 1.6±0.2 mm. The manufacturer developed a test protocol in which aged matrices were soaked in glycine (non-conductive) at 37 °C post-ejection. The outer diameter was measured after a minimum of 24 hours post-ejection. The manufacturer noted that the aged matrices would re-expand back to within the specification at the end of this 24-hour period. In addition, the matrix continued to expand a little more over the next few days. Matrices that were not aged expanded within specification at ejection. Although initial compression of the device could lead to dislodgement of the matrix, this potential for dislodgement of the matrix is more accurately assessed by rate of occlusion as measured in the clinical data.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Early Clinical Studies

1) Tubal Access Study

The applicant studied the ability of investigators to place the delivery catheter via hysteroscopy within the fallopian tube in a total of 43 pre-menopausal women scheduled to undergo tubal ligation. The Adiana procedure was performed except there was no RF energy delivery and no matrix delivery. The endpoint of the study was to determine that the Delivery Catheter was placed at the correct position in the fallopian tube based on visual observation and successful PDA contact. Combined performance (including peri-hysterectomy, pre-hysterectomy, and access studies) over a total of 369 tubal access attempts yielded 336 successful placements (91%).

2) Peri-Hysterectomy Studies

In total, 128 patients were treated with the Adiana System immediately prior to undergoing elective hysterectomy. Histology evaluation of the treated fallopian tube examined uniformity and completeness of epithelial destruction, depth and uniformity of thermal lesion, tubal lesion length, and position of the matrix within the lesion. These studies showed that lesions could be generated reproducibly and that treatment with the Delivery Catheter caused no injury to adjacent organs or structures. The average lesion depth for the final device design was approximately 0.5 mm and average lesion length was approximately 5 mm. During these studies there were no adverse clinical events.

3) Pre-Hysterectomy Studies

The applicant also conducted pre-hysterectomy studies to evaluate treatment protocol, placement rate, tubal patency, patient tolerance, and tissue ingrowth. In the pre-hysterectomy studies, the Adiana procedure was performed on women scheduled to undergo hysterectomy 6 to 12 weeks after the Adiana procedure. Multiple lesion parameters, matrix configurations, and device designs were investigated with 23 patients during the course of several Pilot Studies. Once a final treatment protocol and matrix configuration were selected, a series of 42 patients was evaluated in the Pivotal Pre-Hysterectomy Studies. Tubal patency was evaluated *in vivo* by HSG and *in vitro* by a retrograde salpingogram. The success rate for placement was 65/72 or 90%. Patient tolerance was good and 100% of the matrices placed were retained. Histological evaluation showed abundant blood vessels, mild inflammation, and few layers of fibrosis in the tissue ingrowth.

Major Clinical Study of Safety and Effectiveness

The applicant performed a single major clinical study to establish, with reasonable assurance, the safety and effectiveness of the Adiana Permanent Contraception System for female sterilization. The study was conducted in the U.S., Australia, and Mexico under IDE # G020172. Data from this clinical study were the primary basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between November 18, 2002 and May 4, 2005. The database for this PMA reflected data collected through July 31, 2008 and included 770 subjects (See Figure 4). There were 14 U.S. sites and 2 international sites (Australia and Mexico sites enrolled 143 patients). The Evaluation of the Adiana System for Transcervical Sterilization using Electrothermal Energy in Women Aged 18-45 (EASE) study was a prospective, single-armed, multicenter, international trial.

The primary endpoint of the study was the pregnancy rate during the 12-month Wearing Period, and was summarized with descriptive statistics including sample size, frequency counts, percentages, and 95% one-sided confidence intervals based on SAS® (version 8.2 or later) PROC LIFETEST, which utilizes life-table methods. Additionally, the pregnancy rate was determined for the entire cohort at the 24- and 36-month time points using the same life-table methods.

It was the goal of the study that no fewer than 400 US patients be evaluated for the primary study endpoint (pregnancy within the first 12 months of reliance on the Adiana System). To achieve this goal, and to permit adequate evaluation of the new catheter handle, the study was approved to enroll 650 patients at 15 institutions in the U.S. Additionally, the study was expanded to enroll 100 patients in Australia and 100 patients in Mexico. The FDA approved an increase from 500 to 650 subjects in 2005. No site was permitted to enroll more than 20% of the total patients enrolled in the study.

For comparison, findings from the U.S. Collaborative Review of Sterilization (CREST study) were used as a qualitative benchmark (see http://www.quinacrine.com/archive/pete96.pdf). The CREST study provides contraceptive failure rates for 10 years post-sterilization.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the EASE study was limited to patient who met the following inclusion criteria:
   - Women aged 18 to 45
   - Women who are seeking permanent contraception
   - Women who are at risk of becoming pregnant

- Willing to risk becoming pregnant when relying on the Adiana device for contraception
- Relatively normal uterine cavity, uterine wall thickness, and uterine size as demonstrated by pelvic sonography
- Willing to keep a coital/menstrual log
- Have at least one confirmed pregnancy and one living child
- Monogamous relationship with partner who has proven fertility
- Sexually active (at least 4 acts of intercourse per month)
- Willing to use alternate contraception (either a barrier method or oral contraceptive pills during the three months following device placement prior to permission to rely on the Adiana device for contraception
- Willing and able to maintain regular contact with the investigator
- Women with regular, cyclic menses within 2 months prior to the device placement procedure
- Able to provide informed consent
- [added after start of the trial] Any patient relying on Depo Provera (or other long term continuous hormonal treatment) must have received their last treatment at least 5 months prior to device placement AND must have had two normal, cyclic menses prior to device placement

Patients were not permitted to enroll in the EASE study if they met any of the following exclusion criteria:

- Women who are unsure of their desire to end their fertility
- Presence of gross genital infection, including sepsis
- Presence of chlamydia, gonorrhea, or syphilis
- Presence of genital cancer (note: CIN1 is acceptable)
- Intra-uterine pathology which would prevent optimal access to the tubal ostium and intramural portion of the fallopian tube, such as large submucous fibroids or uterine adhesions
- History of chronic pelvic pain, prior ectopic pregnancy, or fallopian tube surgery, or currently diagnosed severe dysmenorrhea, severe dyspareunia, endometrioisis, adenomyosis, or pelvic inflammatory disease
- Women with unresolved tubal, ovarian, or endometrial pathology
- Uterine neoplasia or precursors to neoplasia
- Dysfunctional uterine bleeding or intermenstrual bleeding within the prior three months
- Women who have not had at least two normal periods after the following events: irregular periods treated with oral contraceptives that have since been discontinued, IUD removal, childbirth, or termination of pregnancy
- Currently taking immunosuppressive medications including steroids
- Pregnancy
- Uterine perforation within the last 3 months
- Contraindications for surgical methods of sterilization
- Less than three months have passed since the last delivery or abortion

2. Follow-up Schedule

The EASE clinical trial had two phases: 1) the "Waiting Period" after successful hysteroscopic placement of the matrices in the tubes and, 2) the "Wearing Follow-Up Period" after tubal occlusion was confirmed. The Waiting Period was the time period between matrix placement and the 3-month visit, during which women were instructed to rely on alternative contraception. At the 3-month Waiting visit, a hysterosalpingogram (HSG) was performed to evaluate tubal occlusion. Investigators were instructed to instill contrast media at a pressure of 150 mm Hg, and that the pressure should not exceed 200 mm Hg at any time. A pressure limiting device (Bonchek Vein Distension System) was recommended to limit distension pressure. If the HSG evaluation showed bilateral tubal occlusion, women were instructed to discontinue alternative contraception, subsequently entering the Wearing Follow-Up Period and relying only on the Adiana System for contraception. If the HSG showed tubal patency or equivalent findings, women were given the option to wait an additional 3 months for a second HSG to see if blockage would occur. Alternatively, they could exit the study and seek another contraception method.

The visits in the study are described as follows:

Matrix Placement

Women underwent the Adiana Procedure typically with local anesthesia alone or with IV sedation. Following the placement procedure, women were assessed for pain and satisfaction with the procedure.

Waiting Period

Women were then seen at periodic evaluations during the Waiting Period as detailed below:

48-Hour Phone Visit

A telephone visit was completed 48 hours after the procedure in which women were asked to complete a series of questions to evaluate recovery and satisfaction. This visit served as a reminder of the need to rely on alternate contraception and to assess any adverse events.

1 -Week Office Visit

This visit included:

- pelvic and physical exam;
- verification of partner fertility and coital activity;
- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs;
- questions on satisfaction, adverse events, concomitant medications, etc.; and,
- Transvaginal Ultrasound (TVUS) to evaluate matrix location.

1 -Month and 2-Month Telephone Visits

Phone follow-up visits were scheduled for 1 and 2 months following the procedure. These visits included:

- verification of partner fertility and coital activity;
- satisfaction and comfort;
- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs; and
- adverse events or unusual symptoms.

3-Month Office Visit: End of Waiting Period

Women were then seen at the 3-month post-device placement follow-up visit.

This visit included:

- pelvic and physical exam;
- pregnancy test;
- verification of partner fertility and coital activity;
- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs;
- questions on satisfaction, adverse events, concomitant medications, etc.;
- TVUS to evaluate matrix location; and,
- HSG to evaluate tubal occlusion.

Wearing Period

Women were then seen for scheduled office follow-up visits at 3, 6, 9, and 12 Months of reliance on the Adiana System for contraception. This follow-up period was later extended to ten years. These visits included:

- physical exam;
- pregnancy test (at 12 months);
- pelvic exam (at 12 months);
- verification of partner fertility and coital activity; and sole reliance on the Adiana System;
- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs; and
- questions on satisfaction, adverse events, concomitant medications. etc.

Phone and office long-term follow-up visits were scheduled for 18 months, and 2, 3, 4, and 5 years. This follow-up period was later extended to ten years. Office visits included:

- physical exam (at years 2, 3, 4, and 5)
- verification of partner fertility, coital activity, and sole reliance on the Adiana System;
- questions regarding comfort and overall satisfaction;

- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs; and
- questions regarding adverse events or unusual symptoms.

3. Clinical Endpoints

For safety, the study gathered all reports of adverse events from the Intent-to-Treat population.

For effectiveness, the primary endpoint for the study was:

- Pregnancy within the first 12 months of reliance on the Adiana System

The secondary endpoints of the clinical trial were:

- Device placement rate
- Patient satisfaction and comfort with the placement procedure
- Patient satisfaction and comfort with device wearing
- Safety of device placement procedure
- Safety of device wearing

With regard to success/failure criteria, the study is powered to have an 80% chance of stating the true failure rate is less than 5%, with a 95% confidence. This would yield a minimum effectiveness rate of 95%.

B. Accountability of PMA Cohort

Of 770 subjects enrolled in the EASE study, 645 women underwent the procedure, and 570 entered the one-year reliance period after a successful HSG. Eighty-six percent (553/645) of the subjects were available for analysis at the one-year effectiveness evaluation (see Figure 6).

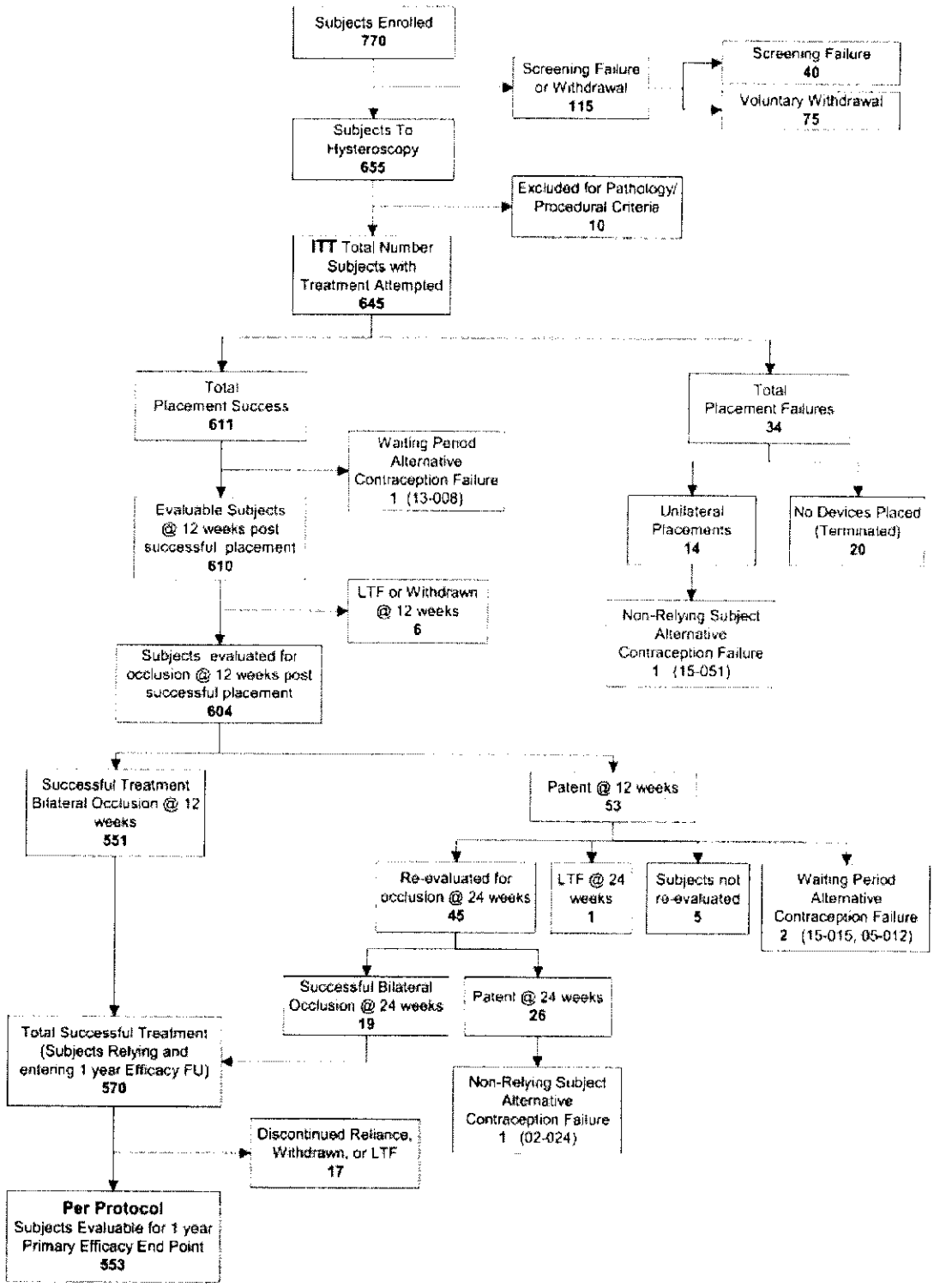

Figure 6: Patient Disposition Flowchart though Primary Endpoint (Total)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are presented in the following table.

Age (mean years)	31.5
Age group	
18-27 years	24.2%
28-33 years	47.7%
34-45 years	28.1%
Race	
Caucasian	488
Hispanic	98
African American	47
Other	12
Gravidity (mean, range)	2.9 (1-9)
Parity (mean, range)	2.2 (0-7)
Weight (mean, range [lbs])	161.8 (98.0-355.0)
Height (mean, range [in])	64.7 (51.3-74.0)

Table 2: Age Distribution and Patient Demographics (N=645)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intent to treat cohort of 645 patients during the waiting period and the initial 12 month reliance period. The key safety outcomes (adverse events) for this study are presented below in tables 3 and 4.

The table below shows adverse events and side effects as a result of the hysteroscopic placement procedure in the clinical trial, reported at an event frequency greater than 0.5%.

Table 3: Adverse Events reported on day of placement procedure (N=645 subjects)

Event	Number	Percentage
Cramping	165	26%
Vaginal Spotting	79	12%
Post-procedural Bleeding	65	10%
Pelvic Pain	58	9%
Back Pain	52	8%
Nausea	30	5%
Headache	28	4%
Vomiting	16	2%
Post-procedural Pain	15	2%
Other	22	3.4%

- Only moderate – severe side effects reported. Some subjects may have reported more than one side effect.
- Eight of the 645 subjects had two procedures.
- "Other" includes events that occurred at a rate > 0.5% and ≤1%: arthralgia (7), dysuria (6), abdominal distension (4), post-procedural discharge (1), vaginal discharge (2) and vasovagal reaction (2).

One event related to the hysteroscopic procedure (hyponatremia), required intervention with medication prior to patient discharge on the day of the procedure. All other events were mild in nature and resolved within a short duration.

The majority of women in the clinical trial reported that the procedure was well tolerated and that any discomfort or pain experienced during the procedure was the same as or less than they expected. Following the procedure, pain was managed with oral analgesics.

The table below summarizes all adverse events in the clinical trial reported to be at least possibly related to the Adiana matrices or placement procedure during the first year of reliance on the Adiana System (up to approximately 15 months post-procedure).

The most frequently reported adverse events in the first year that did not prevent women from relying on the Adiana System were cramping unrelated to menses (6%), dysmenorrhea (5%), vaginal bleeding (4%), back pain (3%) and pelvic pain (3%). All other events occurred in less than 3% of the women.

Table 4: Adverse Events by Body Systems, First Year of Reliance[1,2]
(N=625 patients implanted with a least one device)

Adverse Events by Body System	Number	Percentage
Abdominal:		
Abdominal pain	2	<1
Nausea	4	1
Vomiting	3	<1
Musculoskeletal:		
Back pain	21	3
Nervous System:		
Headache	4	1
Genitourinary:		
Amenorrhea	2	<1
Cramping – unrelated to menses	35	6
Dysmenorrhea	32	5
Dyspareunia	5	1
Menorrhagia	9	1
Pelvic pain	19	3
Vaginal spotting	6	1
Vaginal bleeding	27	4
Vaginal discharge	3	<1
Pain/discomfort – uncharacterized:		
Discomfort	2	<1
Pain	2	<1

[1] Only severe events occurring at a frequency ≥0.5% are reported
[2] Percentages are presented by subject frequency

There have been two ectopic pregnancies during reliance on the Adiana System. One patient (during year 1 of reliance) experienced an isthmic ectopic pregnancy, which was successfully resolved by treatment with methotrexate. One patient (during year 2 of reliance) experienced a left ampullary ectopic pregnancy and was managed surgically by salpingectomy. Another serious adverse event occurred during the second year of reliance and involved a moderate to severe case of dysmenorrhea and endometrial polyp, which were successfully resolved by an out-patient polypectomy.

2. Effectiveness Results

The analysis of effectiveness was based on the 645 evaluable subjects at the 12, 24, and 36 month time points. Key effectiveness outcomes are presented in table 4.

Adiana Matrix Placement

A total of 770 women were enrolled in the EASE trial and 645 of these women had treatment attempted with the Adiana System. Of the 645 women in whom treatment was attempted, bilateral treatment success was achieved in 604/645 (94%) after the first procedure and 611/645

(95%) after a second procedure. Of the 34 women in whom bilateral treatment success was not achieved, 29 were tubal access failures that occurred due to patient anatomy issues (e.g., suspected tubal blockages, extremely lateral tube location; uterine adhesions; poor visualization of ostia; and other varied tubal abnormalities). In one case, the treatment procedure was aborted prior to tubal access or device deployment being attempted because the physician could not maintain adequate uterine distension to perform the procedure due to a patulous cervix.

Reliance

Of the 611 women with bilateral placement, 604 were evaluated for tubal occlusion by HSG. Of these patients, 570 (94%) were ultimately able to rely on the Adiana System for contraception. Inability to rely on the Adiana System for contraception was due to tubal patency identified on HSG.

Non-Relying Pregnancies

There were 7 non-relying pregnancies reported in the EASE trial (pregnancies occurring due to failed alternative contraception during the Waiting Period or after instruction not to rely on the Adiana matrices following unsuccessful treatment; or the patient's choice to discontinue reliance and pursue *in vitro* fertilization). None of these 7 women became pregnant while relying on the Adiana matrices for contraception. Four of these pregnancies resulted in normal term deliveries, one was electively terminated, and two subjects had unknown outcomes.

Effectiveness

A total of 553, 510, and 481 patients have been followed for 1, 2, and 3 years of reliance, respectively (as of July 31, 2008). During the one-year follow-up period, there were six pregnancies among women told to rely on the Adiana system, of which three were attributable to physician error (misinterpretation of HSG results). During the two-year follow-up period, there were three pregnancies attributable to method failure. The table below presents the contraceptive failure rates for the EASE clinical trial, as of July 31, 2008.

Table 5: Contraceptive Failure, First, Second, and Third Year of Reliance

Contraceptive Failure of Adiana Permanent Contraception System				
	# of subjects[1]	# of pregnancies	% pregnancies[2]	95% confidence bound[3]
Year 1	553	6	1.1%	0.6-2.1
Year 2	510	3	1.6%	0.9-2.8
Year 3	481	0	1.6%	0.9-2.8

[1] number of subjects reaching evaluation for that period
[2] cumulative pregnancy proportions
[3] 95% confidence bound using log-log transformation and Peto adjustment

Notes on efficacy table above:

- Of the six relying subjects who became pregnant during year 1, three pregnancies were attributed to misinterpretation of the 3-month HSG.

- Two additional women became pregnant during their fourth year of reliance and one additional woman became pregnant during her fifth year of reliance.

Table 6: Adiana Performance Summary: Pregnancy

	Year 1	Year 2	Year 3
Annualized Pregnancy Rate % (95% 1-sided CI)	1.1 (0.0 – 2.1)	0.6 (0.0 – 2.8)	0 (0.0 – 2.8)
Cumulative Pregnancy Rate % (95% 2-sided CI)	1.1 (0.6 – 2.1)	1.6 (0.9 – 2.8)	1.6 (0.9 – 2.8)

Patient Satisfaction/Comfort

During the long-term follow-up, more than 98% of the patients remained satisfied with the Adiana device and reported "good" to "excellent" comfort with wearing the device. The majority of women returned to normal activities within one day or less after the procedure. There were no requests for matrix removal due to discomfort.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

1-year pregnancy failure rate (U.S.): 4/443 (0.9%)
1-year pregnancy failure rate (Outside U.S.): 2/104 (1.9%)
1-year pregnancy failure rate (Total): 6/547 (1.1%)

There is not a significant difference in pregnancy rates for the US and OUS subjects. However, there was a greater observed failure rate for subjects outside the US than in the US.

Table 7: Age Stratification of Adiana Pregnancy Rates

Age	Number of Subjects*	1-Yr Rate	Long-Term Rates	
			2-Yr Rate	3-Yr Rate
18-27	138	2.26%	3.03%	3.03%
28-33	273	1.12%	1.90%	1.90%
34-45	159	0.00%	0.00%	0.00%

*Based on the number of relying subjects

There is not a significant difference in pregnancy rates with respect to age group. However, there is a trend towards a decrease in pregnancy rate as subjects' age increases.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At the advisory meeting held on December 13, 2007, the Obstetrics and Gynecology Devices Panel recommended that Hologic's PMA for the Adiana Permanent Contraception System be approved with the following conditions:

1. Continue to follow initial cohort of patients from the pivotal study (n=570) out to 10-years;
2. Initiate new cohort (new women, new physicians) in postmarket setting and follow longitudinally to assess generalizability of results ("real world"), endpoint of pregnancy, FDA & applicant to work out sample size details;
3. Special emphasis in patient & professional labeling on uncertainty of long-term effectiveness and risks;
4. Provision in initial cohort PAS for explant analysis in women who undergo hysterectomy
5. Animal study to validate perforation detection feature;

6. Add active control group, preferably transcervical method, to new cohort study

Webpage link to transcripts:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=689

B. FDA's Post-Panel Action

Although the Panel recommended approval of the PMA, they expressed concern about the contraceptive effectiveness of the device as subjects were followed longitudinally. This Panel concern was reflected in the Panel recommendation that a new long-term comparative contraceptive study be undertaken in the post-market setting as a condition of PMA approval. A majority of the Panel members noted that the need for the post-approval study was driven by uncertainty in long-term outcomes (i.e. 3-, 4- and 5-year data) from the pivotal clinical trial cohort. FDA decided that this concern should be resolved before premarket approval. FDA requested that Hologic complete the three-year follow-up on the full patient cohort. These new data were considered as part of the information used to make the final decision on the PMA.

Hologic has agreed to follow the pivotal trial subjects out to 10 years.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

Four serious adverse events have been reported: two ectopic pregnancies, one case of hyponatremia, and one case of moderate to severe case of dysmenorrhea and endometrial polyp. The most common adverse events on day of placement were cramping 26% (165/645), vaginal spotting 12% (79/645), post-procedural bleeding 10% (65/645), pelvic pain 9% (58/645), back pain 8% (52/645) and nausea 5% (35/645). The most common adverse events during the first year of reliance were cramping unrelated to menses (6%), dysmenorrhea (5%), vaginal bleeding (4%), back pain (3%) and pelvic pain (3%). The adverse event outcomes of the EASE study indicate that the device is reasonably safe.

B. Effectiveness Conclusions

Of the 645 women in whom treatment with the Adiana System was attempted, bilateral treatment success was achieved in 604/645 (94%) after the first procedure and 611/645 (95%) after a second procedure. A total of 570 subjects were told they could rely on the Adiana device for contraception (551 after a successful 3-month HSG and an additional 19 after a successful 6-month HSG). Thus, 570/645 or 88% of the women treated were able to rely on the Adiana device for contraception.

The cumulative pregnancy rates after 1, 2, and 3 years of reliance on the device were determined to be 1.1% (0.6-2.1), 1.6% (0.9-2.8), and 1.6% (0.9-2.8), respectively. Thus, results of the major effectiveness study showed the Adiana System to be reasonably effective.

C. Overall Conclusions

The results of laboratory testing provided verification that the Adiana Permanent Contraception System meets the design specifications for electrical, mechanical, sterilization, shelf-life, and thermal safety and performance. Results of *in-vitro* and *in-vivo* biocompatibility testing showed that the delivery catheter and matrix meet the biocompatibility requirements for cytotoxicity, genotoxicity, irritation, acute systemic toxicity, and sensitization. Testing has shown this product to be fully compliant with the biocompatibility requirements of ISO 10993-1. The human clinical data provide a reasonable assurance based on valid scientific evidence that the Adiana System has shown to be safe, acceptable to women, and effective.

XIII. CDRH DECISION

CDRH issued an approval order on July 6, 2009. The final conditions of approval cited in the approval order are described below:

Hologic agreed to evaluate manufacturing yield and defect type for Adiana matrices. Hologic will collect this data over the course of one year after the approval date. The data will be split into four quarters with data from at least ten manufacturing lots from each quarter. Hologic will include a comparison of yield and defect type, comparing pre- and post-manufacturing scale-up. Hologic will submit the results as a single report one year after device approval. Any proposal to broaden or shift specifications will be submitted as a supplement to the premarket approval application.

In addition to the periodic reporting (often referred to as annual report) requirements, Hologic agreed to conduct the following post-approval study to obtain additional safety and effectiveness information of the Adiana Permanent Contraception System:

Hologic agreed to continue follow-up of the patients enrolled in the premarket EASE trial for ten years from the point of the three-month confirmatory HSG. This post-approval study will be a prospective, single armed, multi-center study. The primary study objective is to determine the yearly pregnancy rate from year 4 through year 10 of follow-up, in subjects who underwent successful bilateral treatment and who demonstrated tubal occlusion (by HSG). The secondary objectives are to evaluate subject satisfaction and comfort with device wearing, and device

safety at 4 through 10 years of follow-up. The primary hypothesis test to be evaluated is to show that the pregnancy rates in relying subjects at the 5-year endpoint is less than or equal to the FDA-accepted performance criteria of 6%. In addition, Hologic agreed to perform an interim analysis for the 4-year endpoint (i.e., the pregnancy rate at the 4-year endpoint is less than or equal to FDA-accepted performance criteria of 5%). Hologic will also provide descriptive statistics showing the pregnancy rates with corresponding 95% confidence intervals with life-table methods with log-log transformation and Peto adjustments for years 6 through 10. There are two additional endpoints of interest in this study: (1) safety; and (2) subject satisfaction and comfort. Relevant adverse events reported during the study will be listed, documenting course, severity, possible relationship to device, and outcome. All reproductive and abdominal adverse events will be reported in the PAS study reports.

Hologic also agreed to make every reasonable effort to limit loss-to-follow-up to be less than 20% at the five year follow-up (with an average yearly loss <5%) and to limit the loss-to-follow-up to a minimum during years 6 through 10. If the follow-up rate is unacceptably low during the 10-year follow-up, FDA will consider other regulatory options to address this problem.

The approved post-approval study protocol is located in PMA Amendment 12.

Post-approval study reports will be submitted every six months for the first two years and then annually until the study is completed. The results of the post-approval study must be reflected in the labeling (via PMA supplement) when the study is completed. For details on how to handle the post-approval study reports, please see guidance document "Procedures for Handling Post-Approval Studies Imposed by PMA Order", located at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071013.pdf.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.