

FDA Executive Summary

*Prepared for the
December 13, 2007 meeting of the
Obstetrics & Gynecology Devices Panel*

P070022
Cytoc Surgical Products
Adiana Transcervical Sterilization System

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Table of Contents

I.	Proposed Indication for Use.....	3
II.	Device Description and Principle of Operation.....	3
a.	Matrix.....	4
b.	Delivery Catheter.....	5
c.	Radio Frequency Generator.....	8
III.	Preclinical Studies.....	10
a.	Preclinical Testing.....	10
i.	<i>In Vitro</i> Studies.....	10
ii.	Animal Studies.....	12
iii.	Mechanical Testing.....	13
iv.	Electrical Safety/EMC Testing.....	14
v.	Software Testing.....	15
vi.	Thermal Testing.....	15
vii.	Toxicological Testing of Patient-Contacting Materials.....	15
viii.	Sterilization.....	16
ix.	Packaging.....	16
x.	Shelf-Life Testing.....	17
b.	Preclinical Review Issues.....	17
IV.	Clinical Studies.....	18
a.	Tubal Access Study.....	18
b.	Peri-Hysterectomy Studies.....	18
c.	Pre-Hysterectomy Studies.....	22
d.	Pivotal Clinical Trial.....	23
e.	Clinical Review Issues.....	37
V.	Issues for Panel Consideration.....	40
VI.	Appendices – Further Details.....	42
a.	Appendix I – Animal Studies Conducted.....	42
b.	Appendix II – Toxicological Tests Conducted.....	47

I. Proposed Indication for Use

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

II. Device Description and Principle of Operation

The Adiana Transcervical Sterilization System consists of three principal components:

- silicone matrix (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 Transcervical Sterilization 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 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.

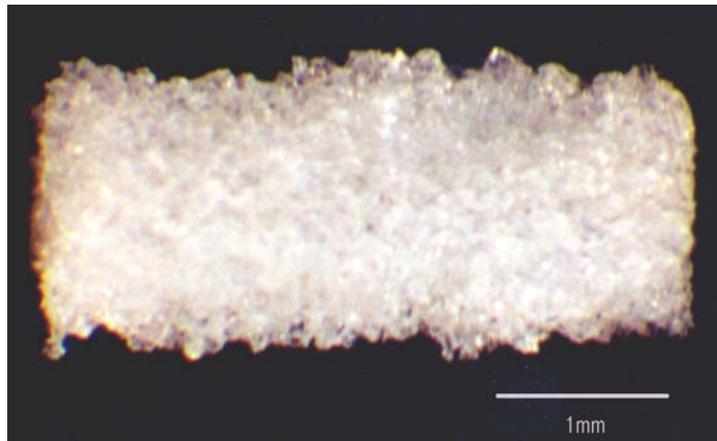
Once placement inside the intramural section of the fallopian tube is confirmed, the distal tip of the catheter delivers RF energy to the electrode array. Thermocouples in the catheter tip are used to maintain a constant temperature of 64°C for 60 seconds (maximum of 120 seconds of treatment per tube 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

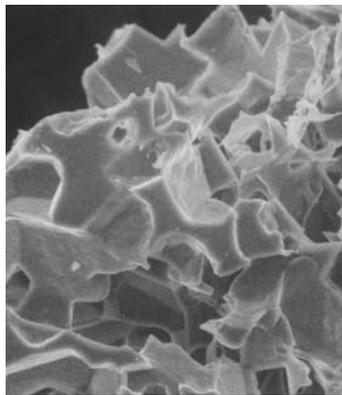
encourages a tissue ingrowth response (i.e., wound-healing response). The implanted matrices provide attachment sites for tissue ingrowth, which secures the matrices in place by filling the voids in the implant. The physician conducts a hysterosalpingogram (HSG) three months after matrix placement to confirm contraceptive tubal blockage.

a. 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. After deployment, the matrix is approximately 3.5 mm in length and 1.6 mm in diameter. See photomicrographs below.



Entire matrix side view



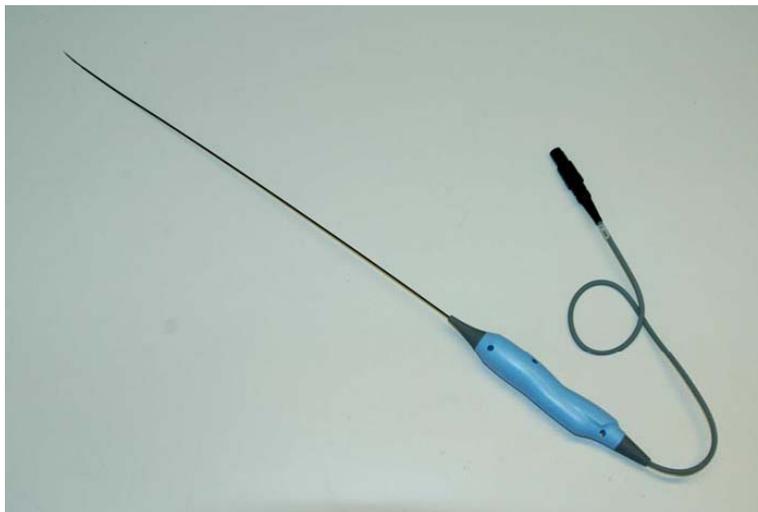
Close-up view of matrix showing random architecture of pores

b. Delivery Catheter

The catheter described below is the current version of the catheter [redacted] introduced into use on September 10, 2004. It was used in [redacted] of the last 310 patients in the pivotal clinical study.

The delivery catheter contains one pre-loaded matrix, and it is used hysteroscopically to introduce and deploy the matrix into the fallopian tube. The delivery catheter includes an electrode sheath configuration at its distal end and a handle at its proximal end. The electrode array consists of four stainless steel bands collinearly 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 0.060 + 0.005 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 [redacted] lid.



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.

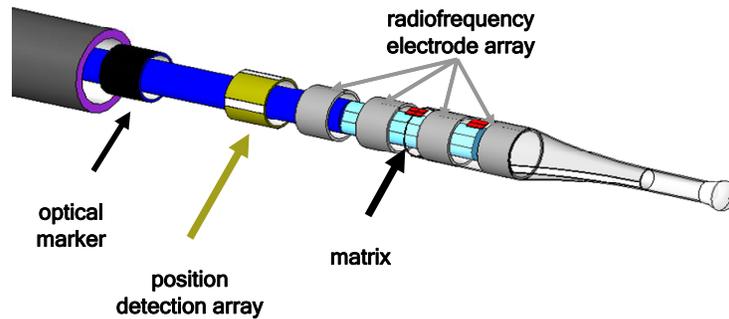
The matrix release mechanism consists of a pre-loaded spring and a fluid filled dampener that are assembled into a sliding mechanism. The slide mechanism includes a latch that prevents any motion until activated by the user. Depressing the button releases the latch, allowing the sliding hub to retract 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 electrode sheath assembly, and a black polyurethane plastic band (black visual position mark) located at the distal 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.

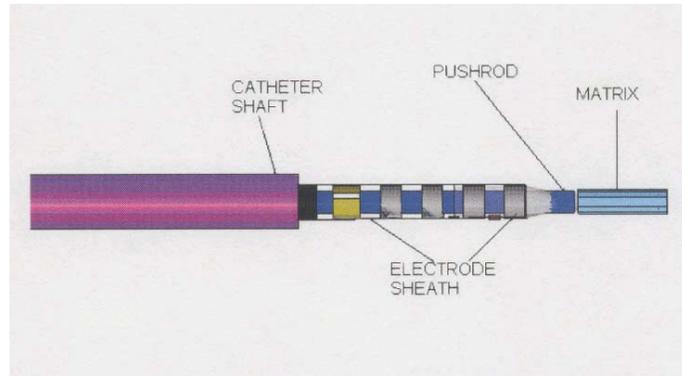


Delivery Catheter (Distal Tip)

The bipolar electrode sheath assembly is 6.0 ± 0.5 mm in length and is comprised of four stainless steel band electrodes (0.047 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 observes the electrical impedance created by the current traveling through the tissue. When a preset threshold 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 are 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.



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.

c. 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. There are no user-selectable settings for power, energy, or time. All treatment parameters are automatically controlled. Treatment parameters of the RF generator are controlled at 64°C for 60 seconds using a temperature controlled feedback system.

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.



RF Generator

Split Introducer

A split introducer is packaged with the Adiana Transcervical Sterilization System as an accessory to the device. The split introducer is a 2.4 inch long hollow polypropylene tube that is placed into the hysteroscope to aid insertion of the delivery catheter (i.e., prevent damage to the tip of the delivery catheter during insertion into the hysteroscope).

Design Changes during Study

The delivery catheter was modified during the course of the pivotal clinical study. (This study is discussed in Section IV.)

- Change to the push rod to add an internal spring coil
- New handle design – The new handle incorporates a push button release instead of a thumb operated plunger to retract the sheath. Added a spring and dampener to provide for sheath retraction.

The old handle design [redacted] was used to treat 335 patients and the new handle design [redacted] as been used to treat 310 patients. These changes wou [redacted] pected to affect the overall effectiveness of the matrix once it was placed. Data from the study showed that the use of these two delivery catheter designs had similar rates of tubal access (95.5% revised catheter versus 93.6% original catheter). The difference was not statistically significant.

Design Changes after the Study

Several changes were made to the device after the pivotal clinical study was completed.

- Change to push rod - The tip of the push rod was changed from domed to slightly concave.
- Electrode band spacing - The inter-band spacing of the most distal two bands was changed from 0.029±.010 in. to 0.024+0.002/-0.003 in.
- Foot switch - Changed to a pneumatic foot switch to initiate a treatment cycle (to obtain IEC 60601-1 compliance) - To accommodate this change, the RF generator was modified to include a pneumatic connector and the operating system hardware was updated to sense this signal.

After device modifications were made to the push rod and band spacing, samples of the modified device were compared to the original device with respect to the ability to release the matrix. The modified devices demonstrated a reduction in failure to release.

III. Preclinical Studies

a. Preclinical Testing

i. In Vitro Studies

Aadiana Feasibility Study: Radiofrequency Generator Comparison Study (Vol 1, pages 172-175, 179-191, 309-362)

The sponsor undertook a series of *in vitro* experiments conducted over a two-year period to assess the feasibility of the Aadiana procedure. The study objectives were 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) evaluate the tissue response to various levels of RF energy; and 3) to evaluate different delivery catheter and electrode configurations. The experiments were conducted using uteri that were obtained following elective hysterectomy. Each investigation tested and validated treatment temperature, lesion formation, amount of tissue ablation, matrix delivery, use of a coating on the delivery catheter to facilitate access, and equivalence of the RF generator to that of a commercially available one (Radionics RFG3C). Individual test reports for

each of these studies are not available; however, Volume 1, pages 315-347 and pages 348-362 contain summaries of each test conducted.

Based upon these tests, the sponsor concluded the following:

- 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 (Vol 1, pages 315-347) 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 reported to be uniform and reproducible.
- The company has also conducted a meta-analysis (Vol 1, pages 184-189) on all *in vitro* results where the 64°C for 60 seconds treatment cycle was used (i.e., studies 6, 9, 11, and 14 shown on pages 315-347 of Vol 1, and studies 14 and 15 shown on pages 342-362 of Vol 1). Analyzed together, the company reported an average 93% epithelial ablation rate with a range of ablation from 35 to 100%. The sponsor also reported that 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 Aadiana RFG (Software Revision B) and the Radionics RFG had similar results in relation to lesion depth, lesion length and percent epithelial ablation.

As part of their assessment of this data, the company stated that the ingrowth model is not sufficiently understood to quantify the acceptable level of destruction; however, uniform destruction over the greatest area is desirable, but not necessarily required. In addition, the sponsor noted that it is important to recognize that all of the women in these studies were undergoing hysterectomy for clinical indications. The impact of the underlying disease processes on the application of RF energy and tissue ingrowth patterns is unknown. The sponsor believes that the apparent difference in ablation rate is most likely due to the underlying disease states, as well as variation in histological staining and identification of cellular destruction.

ii. Animal Studies

The sponsor employed two different general protocols used in the development of the Aadiana System.

1. Short term – evaluate ingrowth and tubal occlusion.
2. Long term – evaluate pregnancy prevention and conduct histological analyses.

For these studies, the rabbit model was used in the assessment of acute RF performance, tissue ingrowth into the silicone matrix, fallopian tube occlusion and pregnancy prevention.

One short-term study was conducted to evaluate ingrowth characteristics and ability to cause tubal occlusion. Two longer-term studies, lasting 12 months, evaluated the ability to occlude fallopian tubes and prevent pregnancy. Longer term studies included histological analyses and tubal patency testing as well as breeding tests to assess the ability to prevent pregnancy.

The short-term study was conducted 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 company 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.

Results of the longer-term studies showed that pregnancy was prevented in all rabbits treated with the Aadiana 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 sponsor concluded that the primary goals of the animal studies were accomplished and that the Adiana procedure could be considered to be effective when the matrices were appropriately placed within the lumen of the oviducts and appears to be effective following implantation for one year.

A summary of each animal study presented in support of this PMA can be found in Appendix I of the Executive Summary.

iii. Mechanical Testing

The sponsor conducted a battery of mechanical tests 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 on the implantable matrix included the following tests:

- visual inspection - assessed under magnification (30x) for any irregularities or damage to the porous surface;
- dimensional inspection - measurements included length and diameter; and
- tensile testing (included some samples initially subjected to compression testing)

The testing of the delivery catheter included the following tests:

- visual inspection;
- dimensional inspection;
- connectivity/insulation;
- repeated hysteroscope insertion and removal;
- compressive loading;
- device rotation;
- fluid exposure (soak) & shaft leak test;
- lesion formation and release actuator;
- electrode tensile strength;
- rotational turns to failure;
- electrode sheath / polyimide junction tensile;
- catheter shaft to strain relief tensile;

- push rod crimp joint tensile; and
- push rod to chassis tensile.

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

iv. Electrical Safety/EMC Testing

The manufacturer conducted the following tests on the delivery catheter (current version):

- 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 appears to be 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)

The device passed all tests.

During recertification to IEC 60601 in late 2005, it was discovered that the auxiliary foot switch used on the RF generator would not be IEC 60601 compliant. The following changes were made to the generator to achieve compliance:

- change to a pneumatic foot switch;
- addition of a pneumatic module inside the RF generator;
- change from an electrical connector to a pneumatic connector; and
- changes to the operating system hardware to sense this signal.

The hardware validation and verification testing appears to be thorough and appropriate.

v. Software Testing

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 sponsor stated that there were no user-selectable settings for power, energy or time, in that all treatment parameters are automatically controlled.

The sponsor provided acceptable documentation demonstrating that they have developed the software for this device under an appropriate software development program; that they have performed a 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.

vi. Thermal Testing

The sponsor provided a computer model of the heat distribution from the four electrode bands on the RF catheter that predicted a lesion size of 6.8 mm long and 1.3 mm deep at the electrode midpoint. The Adiana system has all electrode and thermocouple wires situated on the proximal side of the catheter. The computer simulation provided by the sponsor assumes the effect of these wires in potentially generating asymmetric heating is negligible. It is unclear whether the wires could cause asymmetrical heating.

vii. Toxicological Testing of Patient-Contacting Materials

Biocompatibility

A summary of the biocompatibility studies supporting the safe use of the delivery catheter, silicone used to manufacture the matrix, and Split Introducer was provided within the Cytoc Surgical Products Panel Package (see Appendix II). Biocompatibility studies conducted to support the safety of the Adiana Transcervical Sterilization 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, and sensitization testing (the delivery catheter also passed system toxicity testing). Biocompatibility test data supplied for the delivery catheter, the matrix, and the split introducer were acceptable and complete. A complete listing of the biocompatibility testing performed on each component of the Adiana System is provided in Appendix II of the Executive Summary.

viii. 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, Cytac 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 Cytac to demonstrate ongoing control of the manufacturing environment. The sterilization data supplied for this delivery catheter and matrix was acceptable and complete.

ix. Packaging

The Adiana Transcervical Delivery System is comprised of the RF generator and the delivery catheter (with implantable matrix). The RF generator is a non-sterile, reusable component. Packaged separately, RF generators are received from Adiana’s contract supplier, tested and inspected before repackaging and distribution. Packaging Testing results verified that the packaging system for the RF generator is capable of maintaining product function and package integrity, following exposure to simulated conditions of distribution and handling.

The delivery catheter is for single-use and not intended for reuse or re-sterilization by the user. It is packaged in a single tray along with an Accessory Introducer in steam sterilization compatible packaging. Packaging consists of a polycarbonate thermoformable tray and Tyvek®

lid. The components are packaged in a controlled environment and supplied sterile.

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). Testing results verified the thermoformed tray packaging system for the Adiana delivery system was capable of maintaining package integrity, following simulated conditions of distribution and handling.

x. Shelf-Life Testing

Shelf-life testing was conducted on aged products and included functional performance, sterile barrier testing (ASTM F88-07-Seal Strength Testing) and accelerated aging testing (ASTM F1980). 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.

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 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.

The sponsor conducted a 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 “fresh” matrices. A brief summary of this study is presented above in the Animal Studies Section, and a detailed summary is presented in Appendix I of the Executive Summary.

b. Preclinical Review Issues

The information provided to support the one year shelf life, i.e., expiration date, for the Adiana Transcervical Sterilization System raised issues regarding the ability of the matrix to re-expand to the target outer diameter dimension following long term compression within the catheter. The manufacturer believes that it is sufficient for the outer diameter

specification to be met within a 24-hour period following deployment of the aged matrix. However, FDA is concerned that if expansion of the matrix back to specifications takes up to 24 hours, there may be an increased risk of aged samples becoming dislodged or misplaced within the tube during the initial day(s) following implantation. (The noted maximum decrease in outer diameter of aged matrices was 0.2 mm). The panel should consider this issue in response to questions of effectiveness of the device.

IV. Clinical Studies

a. Tubal Access Study

The sponsor studied the ability of investigators to place the delivery device within the fallopian tube in 28 pre-menopausal women scheduled to undergo tubal ligation. The investigators successfully delivered the device in 52 of 56 tubes (93%), as confirmed by clinician response and video review. No adverse events occurred during the study.

b. Peri-Hysterectomy Studies

Three peri-hysterectomy studies were conducted between November 1998 and September 2005:

- 1st peri-hysterectomy study (n = 62), Study No.
(November 1998 – September 2001) (Vol 1, pa 4-374)
- 2nd peri-hysterectomy study (n = 58), Study No.
(December 2003 and July 2004) (Vol 1, pages 374-402)
- 3rd peri-hysterectomy study (n = 8), Study No.
(September 2005)

Peri-Hysterectomy Study

Sixty-two subjects undergoing hysterectomy for benign conditions were treated in the studies were conducted at the . The purpose of this study was to monitor temperature on the fallopian tube serosa (first six subjects in each of the eight studies) and on the fallopian tube epithelium (all subjects). Serosal temperature monitoring was accomplished with a single thermocouple placed immediately under

the serosa at the uterine horns bilaterally. If temperature did not exceed 44°C in the first six subjects, no further thermocouple measurements were to be made in the subsequent subjects.

The following temperature/time combinations were evaluated:

Temperature	Time

was divided into two stages. The goal of Stage 1 was to optimize operating parameters. The goal of Stage 2 was to verify the final time and temperature settings, electrode length and electrode diameter.

Stage 1 Peri-Hysterectomy Testing

Study	Date	Number of	Number of	Temp/Time (°C/sec)	Electrode/ Device Config	Observations

* NOTE: This was selected as the final current electrode configuration. Diameter reduced to improve tubal access.

Thirty-one subjects were treated and tubal access was achieved in 51 tubes (51/62 = 82%).

From the Stage 1 results, it appeared that 64°C for 60 seconds was optimal.

In Stage 2, the parameters 64°C for 60 seconds were evaluated in 31 additional subjects, in whom access to 54 tubes was achieved. These subjects were enrolled and treated between December 1999 and September 2001.

Objectives and results for are summarized below.

Objective 1: Ability to apply RF in a controlled manner achieving a desired lesion on the epithelial surface of the fallopian tube without excessive fallopian tube damage or thermal injury to other organs.

The outcomes for this objective were as follows:

Endpoint	Results at 64°C/60 sec
Average maximum lesion depth	0.56mm ± 0.10 mm
Lesion length	5.44mm ± 1.73 mm
Percent epithelial ablation	93% ± 7%
Serosal temperature	Peak 41.7°C (Mean temp rise 1.8°C)

Objective 2: Ability to position the catheter into both tubal ostia using hysteroscopy.

For the 62 subjects enrolled, tubal access was achieved in 105 (85%).

Objective 3: Ability to release matrix from the delivery catheter.

There were two matrix release failures in Stage 1, and no release failures in Stage 2.

Objective 4: Ability to release matrix such that the matrix is implanted in the area of the fallopian tube in which the RF lesion was formed.

This was not a long term study, so matrix retention could not really be evaluated. It appeared that in four cases, the leading portion of the matrix may have been in the tubal wall. It is not clear whether this was an artifact of histological processing.

Objective 5: Ability of matrix to maintain position in the fallopian tube.

During Stage 1, the first clinical use of the matrix, the technique for processing specimens was being developed, so it is not possible to evaluate whether this objective was met. However, in Stage 2, all matrices were identified within the tubal lumen at histology with one exception.

Objective 6: Verify [redacted] e Adiana RF Generator compared with the [redacted] Generator.

This objective was met.

Peri-Hysterectomy Study [redacted]

Fifty-eight subjects were enrolled and treated in a series of five substudies. The purpose of the study was to evaluate the acute safety and performance efficacy of two catheter modifications. The first catheter had a change to the electrode sheath to prevent matrix release failures (N=12). The second catheter design was a new handle design and reduction of the outer shaft diameter from 7 French to 5 French to permit more latitude in use of available hysteroscopes (N=46).

Treatment parameters were 64°C for 60 seconds.

Peri-hysterectomy Study [redacted] objectives were to evaluate the following:

- ability to position catheter into both tubal ostia;
- ability to release matrix in area of tube in which lesion formed; and
- histological evaluation (i.e. depth, length, percent epithelium ablated, matrix position).

The first two studies using the new catheter design failed because of a high number of unsatisfactory matrix releases. The device was modified and in the following two studies (N=17) the delivery catheter performed satisfactorily (33 release attempts).

Histological evaluation showed the following:

Catheter Model and	Mean Max lesion depth (mm)	Entire Lesion Length (mm)	Mean % Epithelial Ablation	Length of 90% Epithelial Ablation (mm)
[redacted]	0.46	5.3	90%	4.5
[redacted]	0.56	5.1	99%	5.6
[redacted] Study 13	0.57	4.5	97%	4.2

Peri-Hysterectomy Study

The September 2005 peri-hysterectomy study was conducted in parallel with the pivotal clinical trial. The purpose of this peri-hysterectomy study was to evaluate the narrowing of existing design specifications for the inter-band spacing between the most distal two bands from 0.029±.010 in. to 0.024+.002/-0.003 in. Eight subjects were treated on September 21, 2005.

The histological evaluation revealed that the average maximum lesion depth of the modified catheter was 0.306±0.061 mm. In comparison, the average maximum lesion depth for the control catheter was 0.262±0.044 mm. The average lesion length for the modified catheter was 5.27±0.57 mm whereas the average lesion length for the control catheter was 4.93±0.34 mm. The differences in lesion depth and length between the two catheters were not statistically significant (Student's t test).

c. Pre-Hysterectomy Studies

The sponsor conducted two sets of pre-hysterectomy studies:

- a series of “pilot pre-hysterectomy” studies; and
- a single “pivotal pre-hysterectomy” study.

Twenty-three women participated in the **pilot pre-hysterectomy** studies. The purpose of this series of studies was to evaluate lesion parameters, matrix configurations, and device designs. Two matrix designs and two ingrowth periods (6 weeks and 12 weeks) were evaluated.

The pilot pre-hysterectomy studies had the following endpoints:

- access rate;
- patient tolerance;
- fallopian tube occlusion;
- tissue response; and
- adverse events.

At 12 weeks (n=8), access rates ranged from 87% to 100%. Tubal occlusion measured by HSG was 100%. Tissue ingrowth scores ranged from 1.51 to 1.62. There were no adverse events (see Vol 2, pages 481-484 for Ingrowth Scoring System).



The **pivotal pre-hysterectomy** study was conducted in two phases. In Phase I there were 18 subjects. After this pre-hysterectomy study was completed and reported to FDA, an IDE for a pivotal clinical trial of safety and effectiveness was approved. Subsequently, the sponsor conducted a second pivotal pre-hysterectomy study, N=24.

In this study, tubal patency was evaluated *in vivo* by HSG and *in vitro* by a procedure developed by the sponsor called “retrograde salpingogram” or RSG.

Combining both studies, 84 tubes (42 subjects) were potentially available for matrix placement. Of these, 72 tubes were attempted (12 tubes were not attempted - 10 tubes were blocked on screening and 2 tubes had hysteroscopic visualization limitations). The success rate for placement was 65/72 or 90%.

Patient tolerance was good. Specifically, uterine cramping, back and shoulder pain and pelvic pain were not elevated compared to baseline. Severity of abnormal bleeding did not increase compared to baseline.

One hundred percent of matrices placed were retained. There were no expulsions. Of the 65 tubes accessed, 63 were occluded at the time of hysterectomy. The mean ingrowth score was 2.31.

Histologic findings are listed below.

- Blood vessels were abundant, indicating that the tissue response was very vascular.
- Surface epithelium was virtually absent in the damaged length.
- Inflammation was mild with “a sprinkling of lymphocytes.”
- There were few layers of fibrosis around the matrix. Only small areas of necrosis were observed.
- In two cases, matrices were found in the wall of the tube.

d. Pivotal Clinical Trial

The sponsor conducted a prospective, single-arm, multi-center study. Seven hundred seventy subjects were enrolled between November 13, 2002 and April 28, 2005 at 16 investigational sites (14 in the US and two international).

Statistical Hypothesis

The study hypothesis, established prospectively, was that the upper bound on the 95% confidence interval for the pregnancy rate after one year of use would be less than 5%. The hypothesis was tested using life table analysis with a one-sided test at a significance level of 0.05.

The sponsor originally planned to enroll at least 500 subjects with the primary endpoint (pregnancy at one year) evaluated in at least 400 subjects. The study hypothesis was based on an assumption of a *true* pregnancy rate of 2.5% and powered to have an 80% chance of showing the pregnancy rate is less than 5% at the one-sided 5% significance level.

The **primary efficacy endpoint** was pregnancy during the first year after beginning reliance on the Aadiana system.

Secondary efficacy endpoints were as follows:

- device placement rate;
- patient satisfaction and comfort with the procedure; and
- patient satisfaction and comfort with wearing the devices.

Although the protocol did not explicitly list pregnancy rates at year-2, 3, 4, and 5 as secondary endpoints, the protocol called for following all study subjects out to the 5-year reliance milestone. In addition, procedure safety endpoints were evaluated.

Inclusion and Exclusion Criteria are listed below.

Inclusion Criteria

- Age 18-45; seeking permanent contraception
- At risk of pregnancy; willing to risk pregnancy while relying on Aadiana
- Normal uterine cavity, wall thickness, and size per ultrasound
- Willing to keep coital/menstrual log; at least one confirmed pregnancy and one living child
- Monogamous relationship with one partner of proven fertility
- Sexually active (at least 4 acts/mo)
- Willing to use alternative contraception (barrier or oral contraceptive pills) during 3-month post-device placement
- Willing to maintain contact with investigator; regular cyclic menses within 2 months prior to device placement
- Able to provide informed consent

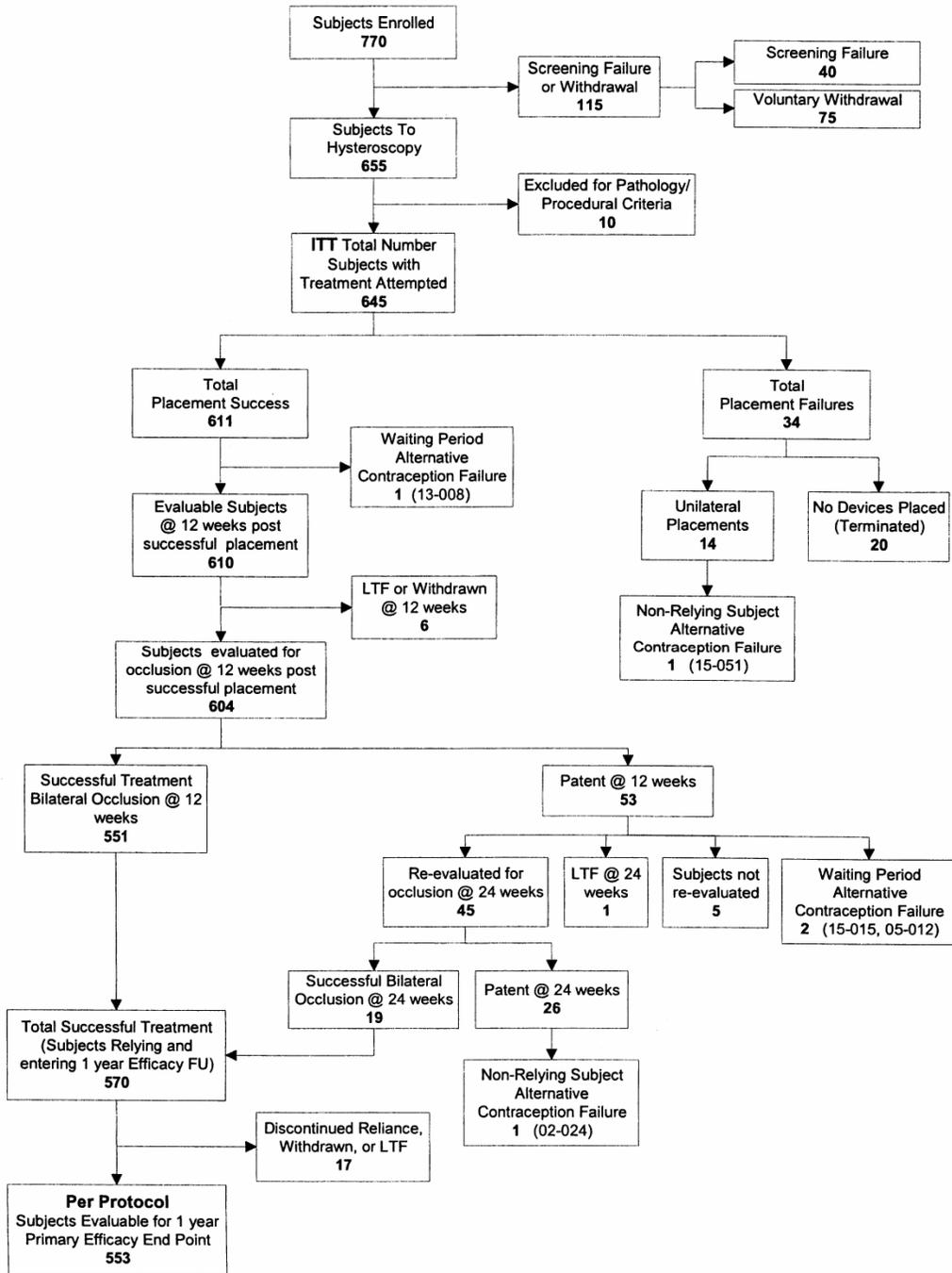
Exclusion Criteria

- Unsure of desire to end fertility; gross genital infection, including sepsis
- Presence of chlamydia, gonorrhea or syphilis; genital cancer (except CIN I)
- Intrauterine pathology that would prevent access to tubal ostium and intramural portion of fallopian tube, such as large submucous fibroids or uterine adhesions
- History of chronic pelvic pain, prior ectopic pregnancy, fallopian tube surgery, or currently diagnosed severe dysmenorrhea, severe dyspareunia, endometriosis, adenomyosis, or pelvic inflammatory disease
- Unresolved tubal, ovarian or endometrial pathology; uterine neoplasia or precursor
- Dysfunctional uterine bleeding or intermenstrual bleeding within prior three months
- Currently taking immunosuppressive medications including steroids
- Pregnancy; uterine perforation within three months
- Allergic hypersensitivity to iodine; contraindications to surgical sterilization
- Less than three months since last delivery or abortion

Execution of Pivotal Clinical Trial

A total of 770 subjects were enrolled in the pivotal study. After voluntary withdrawals and screening failures, 655 underwent hysteroscopy and 645 underwent attempted Aadiana procedure (528 subjects in the US and 117 outside the US). Following successful placement and the three-month HSG confirmation, 553 subjects contributed to the one-year effectiveness evaluation.

The following flowchart shows disposition of study patients through the one-year follow-up time point.



Non-conductive glycine was recommended for the distension fluid to be used during the Adiana procedure. The study protocol did not prescribe analgesia, leaving this to the discretion of the investigators. The following table indicates the most common analgesia regimens.

	US Subjects N=528	International Subjects N=117	Total Subjects N=645
Oral NSAIDS plus topical	149/528 (28.2%)	60/117 (51.3%)	209/645 (32.4%)
Mild sedation plus oral NSAIDS	71/528 (13.4%)	49/117 (41.9%)	120/645 (18.6%)
IV Conscious sedation	300/528 (56.8%)	3/117 (2.6%)	303/645 (47.0%)

Other procedural medications were utilized as follows:

- prophylactic antibiotics (3.7%);
- antiemetics (38.4%); and
- anticholinergics (8.4%)

The mean duration of the Adiana procedure was 11 minutes and 54 seconds (range 4 minutes and 36 seconds to 50 minutes and 35 seconds).

Subjects were discharged to home on the day of the hysteroscopy procedure. Follow-up took place as follows:

Waiting Period Follow-Up

- 48-hour post procedure telephone contact
- One week post-procedure office visit [pelvic exam and transvaginal ultrasound (TVUS)]
- One month telephone contact
- Two month telephone contact
- Three month office visit
 - Pelvic exam
 - HSG
 - TVUS
 - Pregnancy test
 - Instruction to rely on device if HSG shows tubal occlusion
- Six month tubal occlusion re-evaluation (same as 3-month procedure for subjects with patency at 3 months)

Wearing Period Follow-Up

- Three-month office visit
- Six-month office visit
- Nine-month office visit

- One-year office follow up visit
- 18-month telephone contact
- 24-month office visit
- 36-month office visit
- 48-month office visit
- 60-month office visit

Hysterosalpingography

At the end of the waiting period, TVUS was performed to determine whether the matrices were present and HSG was performed to assess whether the fallopian tubes were completely occluded. Investigators were instructed to instill contrast media at a pressure of 150 mm Hg, and that pressure should not exceed 200 mm Hg at any time. A pressure limiting device was recommended to limit distension pressure.

All HSGs were reviewed retrospectively by a two independent reviewers. These reviewers were blinded to the site clinical investigator's evaluation. Patency was defined as visualization of contrast beyond the matrix. The independent HSG reviewers also commented on the following features:

- cornual filling;
- proximal tube filling; and
- cervical leakage.

Because the matrix was visible on TVUS, ultrasound combined with HSG had the potential to provide assurance that, at a minimum, matrices were in place and finding of occlusion could be corroborated.

There were 198 cases that were initially discrepant between the site investigator and the independent reviewers. Some of these cases led to repeat HSG. In all but 4 cases, the third party reviewer confirmed the finding of occlusion made by the original reviewer. This section of the PMA is still under review.

Study Demographics: Age and Ethnicity

Subjects	Enrolled	Intent-to-Treat	Per Protocol
Number of study subjects	770	645	553
Median age (years)	31	31	32
Age groups			
18-27	25.8%	24.2%	23.9%
28-33	47.3%	47.8%	47.6%
34-45	26.9%	28.1%	28.6 %

	Enrolled	Intent-to-Treat	Per Protocol
Number of Study Subjects	770	645	553
Race			
Caucasian	73.8%	75.7%	76.1%
African- American	8.3%	7.3%	7.6%
Asian			
Hispanic	0.6%	0.3%	0.4%
Other	15.6%	15.2%	14.6%
	1.7%	1.6%	1.3%
Weight, mean (lbs)	162.5	161.8	161.0
Height, mean (in)	64.7	64.7	64.6
History of fibroids	1.9%	1.4%	1.6%

Acute Procedural Success Rate

The ability to perform the Adiana procedure, regardless of whether tubal occlusion was confirmed, was evaluated as “acute procedural success.” Basically, this outcome was an indicator of the likelihood that a woman who desired permanent sterilization and was referred for the Adiana procedure would have undergone successful bilateral device placement on the day of the procedure. Acute procedural success is summarized in the table below.

	US Subjects (N=528)	Int'l Subjects (N=117)	Total Subjects (N=645)
Single treatment	520	117	637
Repeat treatment	8	0	8
Successful bilateral placement on first attempt	498/527 (94.5%)	111/117 (94.9%)	609/644 (94.6%)
Successful bilateral placement on second attempt	7/8 (87.5%)	(no 2 nd attempts)	
No devices placed	19/527 (3.6%)	2/117 (1.7%)	21/644 (3.2%)

Acute procedural success rates on the first attempt were slightly higher than the 94.6% when the investigator performed the “pre-access treatment protocol.” In this version of the procedure, the investigator first confirmed he/she could insert the delivery catheter into both fallopian tubes before attempting to place the device. The successful bilateral placement rate was 95.8% in the 120 procedures performed under this protocol; however, this difference was not statistically significant. However, because it did not appear sufficiently advantageous and because it prolonged the procedure by an average of four minutes, this pre-access protocol was abandoned.

The most common reason for failure to place devices was anatomical. These consisted of suspected tubal blockage (20), extremely lateral tube location (3), uterine adhesions (1), poor visualization of ostia (1) and “varied tubal abnormalities” (4). In six cases, device malfunction prevented placement. In 1/6, the RF generator malfunctioned. In the other five cases, the delivery catheter malfunctioned.

At one week post device placement, TVUS was performed to assess whether the matrices were still in place. Of the 611 subjects who had successful bilateral placements, matrices were visualized bilaterally in 604 (98.9%). This demonstrated excellent short-term retention of the Adiana devices.

TVUS and HSG Results

A total of 770 subjects were enrolled and screened. After withdrawals and screening failures, 655 underwent hysteroscopy and 645 underwent attempted Adiana procedure. Of these, bilateral device placement was achieved in 611. A total of 604 underwent transvaginal ultrasound (TVUS) and hysterosalpingography (HSG) at 3 months post device placement.

Of this 604, a total of 551 (91.2%) had bilateral occlusion. Five of 604 (0.8%) had bilaterally patent tubes.

Fifty-three (53) of 604 showed unilateral or bilateral tubal patency at 3 months. By 6 months post-procedure, 26 still showed at least unilateral patency.

For the intent to treat population (n=645), 551/645 (85.4%) began relying on the Adiana device after the three month evaluation. An additional 19/645 (2.9%) were able to rely after a six month post procedure evaluation. For the subset of the intent to treat population who underwent HSG and TVUS (n=604), 551/604 (91.2%) began relying on the Adiana device after the 3-month evaluation. Similarly, for the subset of the intent to treat who underwent HSG and TVUS (n=604), an additional 19/604 (3.1%) were able to rely following a 6-month post-procedure evaluation.

It is interesting to note that on TVUS, 598/604 subjects had devices visualized bilaterally. From the HSG results, however, we know that 551/604 had confirmed occlusion. Therefore, TVUS should not be the sole basis for assessing the likelihood of tubal occlusion for the purposes of relying on the Adiana System for contraception.

Loss to Follow-Up

Five hundred and seventy (570) subjects were told they could rely on Adiana for contraception (551 after the 3-month HSG and an additional 19 after a 6-month HSG). Of the 570, eleven (1.9%) were lost to follow-up during the one-year efficacy follow-up period. Six subjects were lost to follow-up immediately after being informed of their bilateral tubal occlusion status. Three were followed through the 6-month follow-up visit, and the last two were followed through the nine-month visit.

Contraceptive Effectiveness Following 1-year of Reliance on Adiana

There were eleven pregnancies during the first 15 months following the Adiana procedure. Five of the pregnancies occurred while subjects were instructed to rely on an alternate contraceptive: two pregnancies following placement failure, and three pregnancies following successful placement, but during the waiting period (for tissue ingrowth).

Six pregnancies occurred among 553 subjects following successful placement and HSG showing tubal occlusion. These women were told to rely on Adiana for contraception. The six pregnancies contributed to a one-year failure rate of 1.1% with a 95% CI (0.2, 1.9). Of these six pregnancies, one was ectopic. Retrospective review of HSGs for three of these subjects suggests that the diagnosis of tubal occlusion was in error.

Nevertheless, since HSG evaluation for tubal occlusion is an integral part of the Adiana procedure, these were considered procedure failures.

The sponsor met their prospective statistical hypothesis by demonstrating the true failure rate after one year of relying on Adiana was statistically significantly less than 5% ($p < 0.0001$).

Pregnancies Following the First Year of Reliance on Adiana

Three additional pregnancies occurred during Year 2 of reliance, one of which was ectopic. One additional pregnancy occurred during Year 4 of reliance. Therefore, there have been a total of 10 pregnancies among 553 women who were told to rely on Adiana for contraception based on the 3-month HSG, two pregnancies of which were ectopic.

<i>Contraceptive Efficacy of Adiana Transcervical Sterilization System</i>				
	# of subjects ¹	# of pregnancies while relying	estimated pregnancy rate ²	
			point-estimate	95% confidence interval
Year 1	553	6	1.08%	0.22-1.93
Year 2	321	3	1.82%	0.63-3.02
Year 3	133	0	---	---
Year 4	0 ³	1 ³	---	---

¹ number of subjects having completed evaluation as of the database freeze on March 1, 2007

² estimate based on life table methods

³As of the date of the database freeze on March 1, 2007, no subject had completed 4 years of reliance. One pregnancy was reported in a subject who had begun but not completed her 4th year of reliance.

Notes:

- There were too few subjects who completed years 3 and 4 to accurately determine the estimated pregnancy rates and corresponding confidence intervals.
- Of the six relying subjects who became pregnant during year 1, three pregnancies were attributed by the sponsor to clinical mis-reads of HSG.

Analysis of Long-Term Contraceptive Effectiveness Outcomes in Comparison with Other Methods of Surgical Sterilization (CREST Study Comparison)

The study hypothesis was developed around the number of pregnancies that occurred during the first year after sterilization. It would be impractical to require a sponsor to obtain long-term outcomes data in a pivotal clinical

trial for a new device. FDA requested that the sponsor submit two-year effectiveness data for at least 50% of the study population in order to provide some insight on longer-term performance.

Women seeking permanent sterilization have a range of choices among surgical options. It is reasonable and appropriate to evaluate the Adiana procedure against currently available surgical sterilization options. The best long-term dataset in the literature for making this comparison is from the US Collaborative Review of Sterilization (CREST). This study followed pregnancy outcomes (i.e. failures) following six common methods of surgical sterilization for 8-14 years following the procedure. (Ref: Peterson HB, Xia Z, Hughes JM, Wilcox LS, Taylor LR and Russell H. The risk of pregnancy after tubal sterilization: Findings from the US Collaborative Review of Sterilization. *Am Jour Obstet Gynecol* 1996; 174(4): 1161-1170.)

Life-table cumulative probability of pregnancy for six common methods of sterilization was provided for up to 10 years post-sterilization in the CREST study. The table below gives the pregnancy probabilities for the first four years.

Life-table cumulative probability of pregnancy among women undergoing tubal sterilization by method (cumulative probability per 1000 procedures and 95% confidence interval)

Method	# of ♀ sterilized	Years Since Sterilization			
		1	2	3	4
Bipolar coag	2267	2.3 (0.3-4.2)	4.6 (1.8-7.5)	6.7 (3.2-10.2)	13.1 (7.9-18.2)
Unipolar coag	1432	0.7 (0.0-2.1)	2.3 (0.0-4.8)	2.3 (0.0-4.8)	2.3 (0.0-4.8)
Silicone band	3329	5.9 (3.3-8.5)	7.6 (4.5-10.6)	8.3 (5.1-11.4)	9.0 (5.7-12.4)
Spring clip	1595	18.2 (11.5-24.9)	23.8 (16.1-31.5)	29.1 (20.5-37.7)	30.7 (21.9-39.6)
Interval partial salpingectomy	425	7.3 (0.0-15.5)	15.1 (3.1-27.1)	15.1 (3.1-27.1)	15.1 (3.1-27.1)
Post-partum Partial salp	1637	0.6 (0.0-1.9)	3.9 (0.8-7.1)	4.6 (1.2-8.1)	5.4 (1.7-9.2)
All methods	10,685	5.5 (4.1-6.9)	8.4 (6.6-10.1)	9.9 (8.0-11.8)	11.8 (9.7-14.0)

(Peterson et al., 1996)

The following table provides a comparison of the one year failure rates for the Adiana sterilization method as compared to other sterilization methods evaluated in the CREST study.

One Year Failure Rates Comparing Adiana to CREST Methods*

	Failure per 1000 patients		95% CI	95% CI Efficacy Range
	Number of Subjects	Point Estimate		
Postpartum Partial Salpingectomy	1637	0.6	0.0-1.9	99.81-100
Unipolar Coagulation	1432	0.7	0.0-2.1	99.79-100
Bipolar Coagulation	2267	2.3	0.3-4.3	99.57-99.97
Silicon Rubber Band Application	3329	5.9	3.3-8.5	99.15-99.67
Interval Partial Salpingectomy	425	7.3	0.0-15.5	98.45-100
Adiana	553	10.8	2.2-19.3	98.07-99.78
Spring Clip Application	1595	18.2	11.5-24.9	97.51-98.85
All Methods	10685	5.5	4.0-7.0	99.30-99.60

*based on life table methods

The probabilities in the above two tables are given per 1000 women. To estimate the probability per cent, the numbers in the above tables (including confidence intervals) must be divided by 10. The highest probability of pregnancy is for the spring clip. For that procedure, the cumulative probability of pregnancy per 100 women at one year is 1.82 (95% CI: 1.15-2.49). The Adiana one-year outcome is 6/553 (1.1%, 95% CI 0.2-1.93). It appears that the one-year probability of pregnancy for Adiana is higher than all methods described in the CREST study except for the spring clip.

In the PMA, Cytoc has presented a more detailed systematic comparison of contraceptive effectiveness for the Adiana device, the Filshie Clip, and the Conceptus Essure device in the context of the CREST results (Vol 2, pages 595-632).

It is important to note that transcervical sterilization devices/procedures are relatively new and were not available during the years covered by the CREST study. The first and only approved method for transcervical sterilization is the Essure System approved in September 2002 (P020014). There were no pregnancies during the first year of reliance on the ESSURE device. The one-year cumulative failure rate for the ESSURE phase two cohort and pivotal clinical trial cohorts combined was 0.0% (95% CI 0.0-0.12).

FDA is reviewing alternative methods for presenting these analyses to determine which would be the most appropriate analysis to be included in physician and patient labeling.

Acute and Long-Term Safety in Pivotal Clinical Trial

The secondary study endpoints included safety endpoints. The only serious device-related adverse event during the acute treatment phase was a case of hyponatremia related to excess use of the hypotonic fluid glycine for uterine distension.

A total of 328/645 (51%) subjects reported moderate to severe adverse events on the day of treatment. The adverse events are reported below as a percentage of the number of subjects complaining of the event divided by the total number of subjects (645):

- cramping (26%);
- vaginal spotting (12%)
- post-procedure bleeding (10%);
- pelvic pain (9%);
- back pain (8%);
- nausea (5%);

- headache (4%);
- vomiting (2%); and
- post-procedural pain (2%).

Two ectopic pregnancies (one ampullary and one originally reported to FDA as “cornual”) occurred during the first two years of reliance, one of which was managed medically with methotrexate and the other managed surgically by salpingectomy.

Ten subjects underwent hysterectomy after the Aadiana procedure. Of the ten, four occurred prior to 24 months post placement. Six of the ten hysterectomies occurred between 30 and 48 months post placement. In seven cases, the indication was menorrhagia. In two cases, the indication was dysmenorrhea or pelvic pain. In the tenth case, hysterectomy was performed for cervical neoplasia. FDA is currently reviewing the histology slides from these patients to obtain longer term outcomes data, compared to the pre-hysterectomy studies, on the nature and likely permanence of tissue ingrowth into the matrix. FDA’s preliminary findings on the histology specimens suggest that at time points greater than 3 months post placement, some degree of fibrosis was present, along with chronic inflammatory cells and giant cells.

e. Clinical Review Issues

Pregnancies during Pivotal Clinical Trial

When FDA approved the protocol for the pivotal clinical trial, there were no human contraceptive effectiveness data. Data from the pre-hysterectomy study indicated that tissue ingrowth sufficient for tubal occlusion occurs by 3 months of wearing the matrix. These data supported FDA's conclusion that it was acceptable to proceed to a pivotal clinical trial of the Adiana Transcervical Sterilization System with adequate informed consent.

During 2006, when FDA became aware of pregnancies in the pivotal trial, we requested discussion with the sponsor to ensure that adequate protections were in place for treating pregnancies, especially ectopic pregnancies. The sponsor convened a panel of experts who agreed that Informed Consent Document was adequate, pregnancy was rare, and that no change to the study protocol was warranted. The sponsor did meet with their clinical investigators to inform them of the pregnancies, and elicit the degree of comfort the investigators had with the existing protocol. The investigators agreed to remind subjects at scheduled office visits of the possibility of pregnancy and to provide guidance on the signs/symptoms of pregnancy (including ectopic pregnancy).

Although the sponsor met the statistical hypothesis for the first 12 months of wearing the matrices, pregnancies continued to occur among the pivotal trial subjects into Year 4. Specifically, three pregnancies occurred during Year 2 of wearing. All relying subjects who have not been lost to follow-up will pass the two-year mark for reliance as of December 5th, 2007. No pregnancies have occurred to date during Year 3 of reliance. One pregnancy has occurred in Year 4, however. The data sets for Year 3 and Year 4 are incomplete because the entire relying patient population has not passed these milestones yet.

The last subject in the clinical trial was treated on May 4, 2005, and the last patient to enter the relying population did so on December 5th, 2005. Therefore, her HSG occurred no earlier than August 4, 2005. From this we can calculate that the earliest date for all subjects to reach the 3-year milestone for reliance is December 2008, and 4 years of reliance in December 2009.

Possible Contributors to Sterilization Failure in the Adiana Pivotal Clinical Trial

FDA is continuing to review the pregnancies that occurred in the pivotal trial in an effort to understand why these sterilization failures occurred. The following analysis should be considered preliminary as the FDA review is ongoing.

	Possible Reasons for Sterilization Failures	Preliminary FDA Analysis
1	'Ingrowth Scoring System' not clinically validated	<p>The sponsor employed an "Ingrowth Scoring System" (page 2581, Module 4 Volume 8) to assess the degree of tubal occlusion during the pre-hysterectomy study that preceded the pivotal clinical trial. This scoring system assigned points for the following six parameters:</p> <ul style="list-style-type: none"> • closed vascular spaces; • epithelium; • inflammatory cells; • giant cells; • fibrotic capsule; and • necrotic cells <p>This scoring system has not been employed in any tubal research outside of Adiana. <u>FDA is considering whether this scoring system overestimated the degree to which cellular/vascular ingrowth is predictive of permanent tubal occlusion.</u></p>
2	Catheter and matrix placement in the tube	<p>It is possible that catheter and matrix placement could occur outside of the tubal lumen (i.e. perforate into the uterine musculature) A study by Merchant et al. found that the intramural tube was straight in 26.2-30% of cases, curved in 28.6-30% of cases and convoluted in 40-45.2% of cases. A convoluted tube could theoretically pre-dispose to malplacement of the catheter and matrix.</p> <p>(Reference: Merchant RN, Prabhu SR,</p>

		Chougale A. Uterotubal Junction – Morphology and Clinical Aspects. Int J. Fertil 1983; 28(4) 199-205.)
3	Level of tubal epithelial destruction	Tubal epithelial destruction depends on the ability of the current to contact the epithelium. If the fallopian tube were dilated for some pre-existing reason, the contact may not be even throughout. This is probably very rare. In the sponsor’s report of pathology findings they mentioned that residual epithelium was virtually nonexistent.
4	Dislodgement of the matrix material	It is possible that pressure from the HSG procedure could dislodge a matrix plug with subsequent expulsion from the tube, especially since the surrounding tissue is looser and more vascular.
5	Infection	The role of a post sterilization endometritis with potential extension to the transmural tubal matrix area has not been evaluated. It is possible that it could weaken the occlusion or lead to fibrotic changes. Perhaps this could be studied preclinically in rabbits.
6	Hysterosalpingogram	Tubal spasm may result in a false-positive impression of occlusion.
7	Vascular/Cellular Tissue Ingrowth	<u>The issue of whether the non-fibrotic, vascular and cellular tubal repair present around the Adiana matrix at 3 months post procedure has a potential for becoming patent is under review by FDA.</u> This is difficult to predict since there are no comparable models in the fallopian tube. It is known that successful tubal ligations have shown fibrosis when examined later. Tubal failures have shown residual lumens, recanalizations, or fistulas. There is no real precedent for this type of vascular tissue that forms in the near term (it appears that some fibrosis develops after the first 3 months of tissue ingrowth).

Interpretation of HSG

Three pregnancies that occurred during Year 1 of reliance were the result of misinterpretation of HSG studies. Three subjects were erroneously advised to discontinue alternate contraception and to rely on Adiana. The sponsor has suggested that these pregnancies be categorized separately from “method

failures” which they define to be *bona fide* failure to achieve tubal occlusion without any apparent procedural error or error in interpreting the HSG. If FDA were to accept this argument, the number of pregnancies would drop to three during Year 1 of reliance, lowering the cumulative probability of pregnancy in life table analyses as well as improving the 95% confidence interval on this probability.

Given that 50% of the pregnancies during Year 1 of reliance are attributable to error in HSG interpretation, it will be important to emphasize this skill and offer special training to clinicians who prefer transcervical sterilization to laparoscopic sterilization, but who feel that their training in HSG may be inadequate.

V. Issues for Panel Consideration

1. Changes to the Adiana Transcervical Sterilization System
The sponsor made several changes to the device during and after the clinical trial. The sponsor modified the delivery catheter during the clinical trial (see page 9). The sponsor changed the push rod, electrode spacing, and the RF foot switch after the clinical trial (see page 10).
2. Tissue Ingrowth During 3-month Post-insertion Duration
FDA is continuing to evaluate the nature of the tissue ingrowth into the matrix implant. Specifically, FDA is evaluating whether the vascular and cellular ingrowth observed following three months of device placement (as opposed to fibrotic ingrowth at three months with Essure) is likely to provide long-term effectiveness. It should be noted that there is no real precedent for a loose, vascular tissue ingrowth to achieve fallopian tube occlusion. FDA expects that this question will be answered definitively only with long-term follow-up of study subjects.
3. Safety Considerations
The acute safety profile of the Adiana procedure is reassuring. The most serious adverse event on the day of the procedure was a single case of hypervolemia and hyponatremia that resolved with diuresis. The recommended fluid distension medium for the procedure is glycine, an electrolyte-poor low viscosity fluid used during operative hysteroscopy involving RF. Glycine carries a risk of hyponatremia, therefore training will be important regarding fluid management, especially since some users may not normally perform operative hysteroscopy.

Other acute and longer term (up to one year following device placement) anticipated adverse events included abdominal pain,

nausea, vomiting, back pain, headache, amenorrhea, cramping, dysmenorrhea, dyspareunia, menorrhagia, pelvic pain, vaginal spotting, vaginal bleeding, vaginal discharge, discomfort, and pain. The degree to which these events are related to the Adiana procedure is unknown, especially the longer term outcomes. The rate at which these events were reported are low and in no case was re-admission necessary to manage these events.

The most serious long term adverse events were two ectopic pregnancies. The rate of ectopic pregnancy among sterilization failures in this study was 2/10 or 20%. One ectopic was managed medically (with methotrexate) and the other required salpingectomy. The occurrence of ectopic pregnancies in this pivotal clinical trial highlights the importance of patient counseling regarding the risk that sterilization failure may occur and that if it does, ectopic pregnancy with all of its sequelae is possible.

4. Effectiveness Considerations

The acute procedural success of the Adiana System was reassuring in that successful bilateral device placement on first attempt was achieved in 609/645 (94.6%) subjects. The rate of tubal occlusion as demonstrated by HSG three-month post placement visit was somewhat lower in that 551/604 (85.4%) of subjects with successful bilateral placement who returned for the 3-month evaluation were told they could rely.

Regarding success for the primary endpoint, since the start of the EASE trial in November 2002, ten of 553 women who were told to rely on the Adiana System for contraception have become pregnant. (In three of the ten cases, it appears that errors in interpreting the HSG led to erroneous advice to discontinue alternative contraception and rely on Adiana.) Six pregnancies occurred during the first 12 months of reliance. Three occurred between months 12 and 24, and once occurred between months 36 and 48. Pregnancy outcomes for >24 months of reliance are incomplete.

The sponsor met the primary study hypothesis which was based on all subjects completing 12-months of reliance on the Adiana System. (Under the study hypothesis, 19-20 pregnancies could have occurred during the first year and the hypothesis would still have been met.) Longer term (>12 months of reliance) pregnancy outcomes data were not factored into the study primary or secondary endpoints. This is an important consideration for a sterilization procedure

5. Post Approval Study

The sponsor proposed to continue follow-up of patients enrolled in the premarket cohort (Pivotal Clinical Trial) for up to 5 years. The primary research question that will be addressed is to determine the 3, 4, and 5 year device failure/effectiveness rates.

FDA continues to work with the sponsor to develop a detailed post-approval study (PAS) protocol for the extended follow-up of the premarket cohort to address long-term safety and effectiveness (5-years of follow-up).

6. Training and Labeling

Cytec plans to market devices exclusively to physicians who have successfully completed the Physician Training Program. Physicians must be experienced in the use of operative hysteroscopy or will need to obtain training. Since performing and accurately interpreting HSGs is important to the success of the Adiana Transcervical Sterilization procedure, a separate training program for interpreting HSGs has been developed.

The sponsor provided labeling for the delivery catheter and the RF generator. Cytec provided draft versions of the Summary of Safety and Effectiveness Data, Instructions for Use, RFG Specification and Installation Manual, HSG Protocol, and Patient Manual. Some of these documents are currently incomplete or may need revision.

VI. Appendices – Further Details

a. Appendix I – Animal Studies Conducted

Long Term Implant: Sterilization Method Evaluation (Study
Vol 1, pages 272-307)

The main objective of this study was evaluate whether application of the Adiana System to rabbit oviducts would result in integration of the porous silicone matrix over extended time periods (6 to 12 months). Other objectives included evaluation of differences in matrix retention and placement, tubal occlusion, pregnancy prevention, and ingrowth characteristics between steam sterilized implants.

Animals were randomly assigned to 6-month (n=5) and 12-month (n=6) treatment groups. Rabbits in these groups received RF treatment at 58°C for 60 seconds, followed by delivery of silicone implants (left tube, [redacted] implant; right tube, steam sterilized implant).

Rabbits were evaluated for pregnancy prevention with a single breeding attempt at 5 or 11 months post-implant. Rabbits were euthanized 18 to 21 days after the breeding attempt, and the uterine horns with attached oviducts were removed and assessed.

Results from this study demonstrated pregnancy was prevented in all 11 animals (22 tubes) after treatment with Adiana System. In addition, of the 22 oviducts treated, 21 were shown still to contain the silicone matrix (95% retention). Of these 21 tubes containing the silicone matrix, all withstood the dye pressure test to assess tubal patency.

Four tubes from the 6-month rabbit group were analyzed for the presence of sperm proximal to the silicone matrix using the sperm detection assay. In this study human sperm were placed in the oviduct distal to the silicone implant. Testing showed no presence of sperm proximal to the implant site.

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. Vascular supply was also evident, with the steam sterilized group showing significant counts. Inflammatory cells were similar in steam and [redacted] implants at 6 months, but the 12-month [redacted] implant group showed a marked increase (approximately 3-fold increase) in the number of inflammatory cells, predominantly lymphocytes. The investigators speculated that this effect was caused by some alteration in the matrix associated with the sterilization procedure. It should be noted that the matrix proposed for marketing is steam sterilized.

The sponsor concluded that the primary goals of the study were accomplished and that the Adiana procedure could be considered to be effective when the matrices were appropriately placed within the lumen of the oviducts and appears to be effective for long time periods.

Long Term Implant II: Matrix Length Evaluation (Study [REDACTED])

The main objective of this study was to evaluate whether application of the Aadiana System to rabbit oviducts would result in integration of the porous silicone Matrix over extended time periods (6 to 12 months). Other objectives included evaluation of matrix retention and placement, tubal occlusion, pregnancy prevention, and ingrowth characteristics between matrices of different lengths.

Animals were randomly assigned to 6 month (n=7) and 12 month (n=8) treatment groups. Rabbits in these groups received RF treatment at 58°C for 60 seconds, followed by [REDACTED] m or radiation sterilized) silicone implants [REDACTED] 3.5, or [REDACTED]

Rabbits were evaluated for pregnancy prevention with a single breeding attempt at 5 or 11 months post-implant. Rabbits were euthanized 18 to 21 days after the breeding attempt, and the uterine horns with attached oviducts were removed and assessed.

Results from this study demonstrated that pregnancy was prevented in all 15 animals; however only 28 of 30 possible tubes were treated as rabbit F0243 had no right tube due to a congenital defect, and no implant was placed in the left tube of rabbit F3536 due to procedural difficulties. In addition, of the 28 oviducts treated, all were shown still to contain the silicone matrix (100% retention). All of the 28 tubes containing the silicone matrix withstood the dye pressure test to assess tubal patency.

Histological assessment of tissue samples from rabbits demonstrated that in the tissues examined, all 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. Closed vascular structures (CVS) were [REDACTED] served in tissue surrounding the silicone implants, with the 3.5 and [REDACTED] matrices having higher CVS counts at 6 months than the [REDACTED] im [REDACTED]. By 12 months, CVS counts were similar for all implant [REDACTED]. Inflammatory cells were more prevalent in tissues surrounding [REDACTED] implants at 6 months, but were similar in all implants at 12

The sponsor concluded that the primary goals of the study were accomplished. The standard sized matrix (3.5 mm) gave the highest ingrowth score at 6 months but at 12 months all sizes had similar ingrowth scores and were stated to have little inflammation and necrosis.

Product Validation for Matrices Aged for 1 Year (M060004, Module 2, Appendix 34)

The purpose of this study was to assess the ability of matrices that had been aged for 1 year inside the catheter to expand and support tubal occlusion in rabbits as compared to “fresh” matrices.

Matrices used in this study included ones that had been aged inside the delivery catheter for one year before use, while controls consisted of matrices that were approximately 6.5 months old at the time of the study, but had been stored uncompressed since the time of manufacture.

Treatment of rabbits (n=6/group) receiving implants involved lesion creation with a rabbit catheter using a 60 second, 58°C RF treatment cycle. Three weeks after implant the rabbits were euthanized and tubes collected. Following explant, a visual inspection of the tubes was performed to assess matrix placement and retention. To assess whether occlusion had occurred, a dye passage test was performed, and tubes further processed for histological examination. The results of the study are shown in the table below:

Animal Number	Group	CVS	EPI (%)	Inflam	Giant	Fibrotic	Necrotic	Score	Dye Test

count; Giant=number of giant cells; Fibrotic=presence/thickness of a fibrotic capsule; Necrotic=Existence/degree of necrosis)

Results of the dye test (50 mm Hg for 1 minute, followed by 100 mm Hg for 4 min) 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 more a function of the RF treatment procedure in these animals and likely not related to the matrix.

Based on the results of this study, the company concluded that matrices stored compressed in the delivery catheter for one year gave similar ingrowth responses and showed similar responses when subjected to dye binding testing.

As part of the review of this study we asked the sponsor whether the use of uncompressed matrices that were 6.5 months old might impact the results of this study had the control matrices been tested immediately after they had been manufactured. The company responded that the 6.5 month old matrices were an adequate control for this study as silicone is a relatively stable material and should not have undergone any degradation over the storage period. In addition, these control matrices had not been compressed prior to testing. This response was considered acceptable.

b. Appendix II – Toxicological Tests Conducted

Aadiana Delivery Catheter

Cytotoxicity- ISO Elution Method: Testing showed no evidence of cell lysis or toxicity from the delivery catheter materials.

Irritation - ISO Vaginal Irritation Study: Testing showed both the saline and cottonseed oil extracts to be minimal irritants to the vaginal mucosa tissue of rabbits, as were the control solutions tested.

Sensitization- ISO Maximization Sensitization Study: Testing showed no evidence of sensitization from saline or sesame oil extracts of the delivery catheter or introducer device materials.

Systemic Toxicity- USP and ISO Systemic Toxicity Study: Testing showed no evidence of mortality or systemic toxicity from saline or sesame oil extracts of delivery catheter materials.

Aadiana Matrix

Cytotoxicity - ISO Elution Method: Testing showed no evidence of cell lysis or toxicity from the silicone matrix material.

Sensitization- ISO Maximization Sensitization Study: Testing using saline and sesame oil extracts showed no evidence of the silicone matrix material causing delayed dermal contact sensitization.

Intracutaneous Reactivity- Acute Intracutaneous Reactivity Study: Testing using saline, cottonseed oil, polyethylene glycol and alcohol in saline extracts showed no evidence of significant irritation from the silicone matrix material.

Systemic Toxicity- USP Systemic Toxicity Study: Testing using saline, cottonseed oil, polyethylene glycol and alcohol in saline extracts showed no evidence of mortality or systemic toxicity from the silicone matrix material.

Pyrogenicity – USP Rabbit Pyrogen Study: Testing using a saline extract showed no evidence of increasing body temperatures in rabbits. Therefore, the silicone matrix material is considered non-pyrogenic.

Hemolysis – In Vitro Hemolysis Study: Testing using a saline extract showed no evidence of causing hemolysis in blood samples. Therefore, the silicone matrix material is considered non-hemolytic.

Genotoxicity - Mouse Bone Marrow Micronucleus Study: Testing using saline and sesame oil extracts showed no mutagenic effects of the silicone matrix material.

Genotoxicity - Mouse Lymphoma Assay: Results of this study showed that extracts of the test article were non-mutagenic to the mammalian cell line tested.

Genotoxicity - Bacterial Reverse Mutation Assay: Testing using saline and DMSO extracts in the presence and absence of S9 activation showed the silicone matrix material to be non-inhibitory to growth of tester strains and non-mutagenic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* (strain WP2uvrA).

Implantation – One-Week Rabbit Muscle Implantation- USP Muscle Implantation Study in the Rabbit: Testing showed no significant difference between the control and test materials. The conclusion from this test is that the silicone matrix material did not elicit any toxic effects (non-irritant) on muscle tissue.

Implantation – Twelve-Week Rabbit Muscle Implantation- USP Muscle Implantation Study in the Rabbit: Testing showed no significant difference between the control and test materials. The conclusion from this test is that the silicone matrix material did not elicit any toxic effects on muscle tissue.

Carcinogenicity Testing: The sponsor supplied an adequate justification for not conducting carcinogenicity testing on the matrix.

Reproductive Toxicity Testing: The sponsor has supplied an adequate justification for not conducting reproductive toxicity testing on the matrix.

Split Introducer

Cytotoxicity- ISO Elution Method: Testing showed no evidence of cell lysis or toxicity from the Split Introducer materials.

Irritation - ISO Vaginal Irritation Study: Testing showed both the saline and sesame oil extracts to be non-irritants to the vaginal mucosa tissue of rabbits.

Sensitization- ISO Maximization Sensitization Study: Testing showed no evidence of sensitization from saline or sesame oil extracts of the Split Introducer materials.

Systemic Toxicity- USP and ISO Systemic Toxicity Study: Testing showed no evidence of mortality or systemic toxicity from saline or sesame oil extracts of Split Introducer materials.