Adiana Transcervical Sterilization System
PMA P070022 Panel Pack

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I. INTRODUCTION

I. A. INDICATION FOR USE

1.3.2 Executive Summary: 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.

I. B. GENERAL BACKGROUND INFORMATION

1.3.3 General Background Information

Cytyc began development of the transcervical sterilization system in 1997. Extensive bench testing, explanted human tissue studies and animal use were undertaken to understand and optimize a technique to achieve tubal occlusion in patients. Over the course of the next four years, Cytyc further developed the system and methodology, and in February 2002, submitted information to FDA [redacted] Following this submission, Cytyc met with members of FDA's Obstetrics and Gynecology Devices Branch on February 22, 2002, to discuss the product technology, clinical research results, and a proposed clinical study.

Subsequently, Cytyc submitted an IDE for the Adiana Transcervical Sterilization System on July 2, 2002. This IDE described a pivotal clinical study, entitled "A Multi-Center, Prospective Evaluation of the Adiana System for Transcervical Sterilization Using Electrothermal Energy in Women Aged 18-45 - The EASE Trial". A conditional approval was received on August 2, 2002, and final approval was received on October 16, 2002.

Since that time, Cytyc has submitted the following supplements and notifications to FDA:

Table 1.1: Adiana Transcervical Sterilization System IDE Changes

Submission Number	Date of Request	Description of Changes
[redacted]		

Submission Number	Date of Request	Description of Changes
[redacted]		

Submission Number	Date of Request	Description of Changes
[redacted]		

Submission Number	Date of Request	Description of Changes
[redacted]		

I. C. BRIEF DEVICE DESCRIPTION

1.3.4 Executive Summary: Brief Device Description

The Adiana Transcervical Sterilization System (Adiana System) provides for female sterilization by occlusion of the fallopian tubes via a hysteroscopic transcervical approach.

Adiana Transcervical Sterilization System Components
The Adiana Transcervical Sterilization System is comprised of the following components:

- Delivery Catheter with split Introducer
- Matrix
- Radiofrequency (RF) Generator

1.3.4.1 Adiana Delivery Catheter

The Delivery Catheter consists of a multi-pin connector which is attached to the handle by an 18 inch cable, a plastic handle with matrix-release mechanism and a 40.5 cm catheter shaft. The catheter shaft contains conductors for the thermocouples, RF current-conducting wires, and a matrix-release mechanism. The distal portion of the catheter has four electrodes, two embedded thermocouples and a Position Detector Array (PDA). The Delivery Catheter contains a push button release mechanism which, once triggered by the operator, will automatically release the Matrix with no further action required from the operator. The device is supplied sterile, and is a single use device. The Delivery Catheter is packaged with the split Introducer, which is an accessory to assist in placing the catheter into the operating channel of the hysteroscope. A photograph of the Delivery Catheter is included below in Figure 1.1.

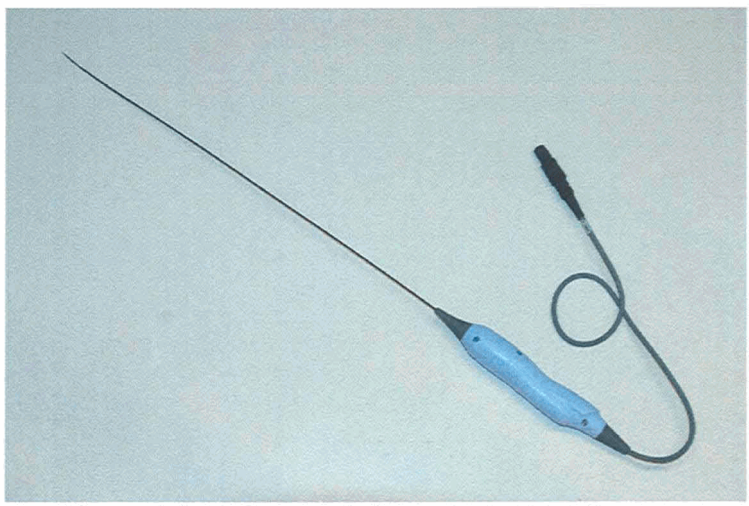
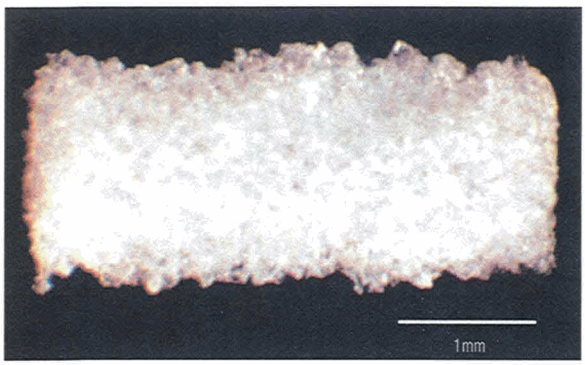
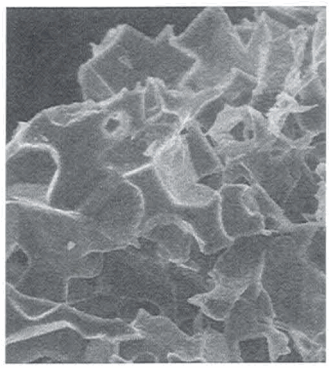


Figure 1.1: Delivery Catheter (FA 011 01)

1.3.4.2 Adiana Matrix

The non-absorbable biomaterial 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 material utilized has a long history of implant applications, and therefore, has a large body of safety information as well as biomaterial testing data. In addition, longer term implant data in animals and humans have shown no adverse tissue effects, with only mild localized responses. The Matrix is shown in Figures 1.2a and 1.22b.





1.2a **1.2b**

Figure 1.2a: Entire Matrix side view
Figure 1.2b: Close-up view of Matrix showing random architecture of pores

1.3.4.3 Adiana Radiofrequency Generator

The Radio Frequency Generator (or "RF Generator") is custom designed for the Adiana procedure. There are no user-selectable settings for power, energy or time. All treatment parameters are automatically controlled. The RF Generator has a LCD front panel display which prompts the operator through the sequence of steps to complete a procedure. It includes accessories: a foot switch for control of certain generator functions and a cable to connect the generator to the Delivery Catheter. The RF Generator is shown below in Figure 1.3.

Figure 1.3: Adiana RF Generator [redacted]

I. D. OVERVIEW OF PRODUCT DEVELOPMENT

I. D. 1. MATERIAL SAFETY TESTING

5. Executive Summary: Testing Contained in Module #1

- Material Safety Testing

Material Safety Testing of the Adiana Delivery Device and Matrix was performed to ensure that raw materials, manufacturing, and sterilization processes have resulted in a biocompatible product. The Adiana Delivery Device is considered a "Surface Contact" device that contacts breached or compromised surfaces (Adiana considers the interior of the fallopian tube "compromised" following lesion formation) with contact duration less than 24 hours. This testing also meets testing guidelines for limited duration contact with mucosal surfaces. The Matrix, delivered by the delivery device, is an "Implant Device", which contacts tissue, with permanent contact duration.

The implanted component, the Adiana matrix, comprised of [redacted] has been tested separately and together with the Delivery Catheter. Additionally, non-carcinogenicity of this material has also been established through [redacted] testing, Adiana bench and animal testing, historical data, and information provided by the manufacturer. Results are further presented in Sections 4.1.2 (Material Safety), Section 4.2 (Engineering/Bench Testing) and Section 4.3 (In Vitro and Animal In Vivo Studies).

Patient contact materials used in various components of the Adiana Transcervical Sterilization System are listed in Table 4.2.

All product biocompatibility testing was performed following steam sterilization. The majority of the testing was conducted by [redacted]

Using its In-growth Scoring System, Adiana has also conducted a series of safety/performance animal studies to evaluate long term safety and efficacy. These studies are described further in Section 4.3. Overall, these studies showed no unusual histological or carcinogenetic implant effects.

After exposure to its steam sterilization cycle, Adiana's Transcervical Sterilization System meets the biocompatibility requirements for cytotoxicity, genotoxicity, irritation, acute systemic toxicity, and sensitization. Results are presented in Section 4.1.2 Material Safety. It has been shown to be fully compliant with the biocompatibility requirements of ISO 10993-1 and is determined to be acceptable.

I. D. 2. ENGINEERING/BENCH TESTING

- Engineering/Bench Testing

Engineering / Bench testing of the Adiana Transcervical Sterilization System has been conducted in order to verify that the design output conforms to the design input requirements described in the product specification. Description and results of bench testing are reported in full in Section 4.2 for the Adiana Delivery Catheter and Matrix (for both the "Current" and "Original" handles). Per agreement with FDA, testing for the RF Generator will be reported in Module #2.

While Material Biocompatibility is addressed in Section 4.1 of this Module, additional information describing patient contact materials is provided in the Material Analysis Section 4.2.2. of the Engineering/Bench Testing section. Product specifications and inspection criteria are described for each patient contact material including Silicone [redacted]; Stainless Steel, Type 316 L; [redacted] Tubing, Extrusion 65D PU; Composite Polyimide tubing with PTFE liner, .056"ID, .002 wall, black; and Lubricious Coating.

Verification test results for the Current Delivery Device (FA 011 01) that were submitted as [redacted] are presented in Table 1.2 below and are described more fully in Section 4.2.3.1 (Engineering/Bench Testing).

Table 1.2: Verification Testing of Current Handle Delivery Device (FA 011 01)

Test	Units Tested	Results:
[redacted]		

All results obtained during this evaluation were acceptable. The results verify that the design output conforms to the design input requirements described in the product specification.

Additionally, two minor interrelated post-trial device modifications to the "Current" Delivery Catheter are described in Sections 2.6.2 and 4.2.3.2. These changes were developed in response to device malfunctions in the field. The band spacing modification and change in shape to the tip of the push rod are both within original product specifications.

Section 4.2.3 of Engineering/Bench Testing also contains description and verification testing for the "Original" Delivery Device and Matrix (Section 4.2.3.4). A description of the Compression Testing that was performed separately on the Matrix as part of the original Design Verification testing is included (Section 4.2.3.5). Finally, a summary of the 5-Day Notice, submission of minor changes to the "Original" Delivery Catheter [redacted] is provided (Section 4.2.3.2.).

I. D. 3. ELECTRICAL SAFETY TESTING

- Electrical Safety Testing

The Adiana RF Generator was designed and developed by [redacted] under contract to Adiana. All product design activities were performed in accordance with [redacted] written product development procedures. [redacted] is in compliance with ISO 13485. In addition, [redacted] will manufacture the Adiana RF Generator. Module 2 will contain a complete discussion of the [redacted] manufacturing facilities, Quality Systems procedures, and Design Control systems. Module 2 will also include a detailed product description and testing verification results for the RF Generator hardware and software.

Electrical Safety and electromagnetic compatibility testing of the Adiana RF Generator was performed on both the Original and Current handle devices. Testing was conducted in accordance with internationally recognized standards by [redacted], and by independent test facilities. Certification of Compliance and/or documentation of successful test results for the Adiana RF Generator are summarized in Table 1.3 below.

Table 1.3: Electrical Safety Test Results

TEST	RESULTS
[redacted]	

I. D. 4. DEVELOPMENT STUDIES: IN VITRO AND ANIMAL

- Development Studies

  Adiana has performed an extensive series of investigations to characterize the safety of the Adiana procedure, to determine the proper device configuration and to define a clinical protocol. This research has focused on all aspects of device performance, including access to the fallopian tube, radiofrequency lesion creation, matrix delivery, host tissue response and in-growth, tubal occlusion and pregnancy prevention. These studies, which are presented in detail in Section 4.3 (In Vitro and Animal In Vivo Studies) are defined below (note that additional human clinical development studies will be presented in Module 4):

  In Vitro Extirpated Uteri Studies:

  These studies utilized extirpated uteri from patients undergoing elective hysterectomy. Following removal, the uteri were used to evaluate catheter handling and performance. In addition, the ability to deliver RF energy and create a superficial thermal destruction of endosalpynx to the epithelial layer in the fallopian tube was evaluated. Histological analysis following treatment in extirpated uteri samples was used to define proper RF treatment parameters.

  Animal Studies:

  The Adiana system was evaluated in the rabbit model. This model was used primarily to assess: acute RF performance, tissue in-growth into the matrix, fallopian tube blockage and pregnancy prevention. Animal studies have confirmed that the Adiana system results in tubal occlusion as demonstrated by rigorous challenge with pressurized fluid. In addition, mating studies performed in rabbits have shown pregnancy prevention at 6 months and 12 months post implant.

I. E. ALTERNATIVE PRACTICES AND PROCEDURES

1.4. Alternative Practices and Procedures

The most common form of contraception in the United States is female sterilization.[8] Annually 600,000 to 700,000 women undergo sterilization procedures.[8] One form of female sterilization involves a mini-laparatomy and a tubal ligation technique which was developed nearly a century ago.[29] Other more common methods utilize laparoscopic techniques which include electrocoagulation or the application of clips or rings to the fallopian tubes.[29] Surgical sterilization procedures have significant disadvantages including equipment costs, facility requirements including resuscitation capabilities, anesthesia, and post-operative pain. Each method of surgical sterilization has method-specific limitations of safety and efficacy.

Due to the limitations of current surgical methods for sterilization, several investigators have proposed alternative methods for transcervical sterilization. Unlike tubal ligation, which often requires general anesthesia and multiple-day recovery times, it was believed that these new techniques might be performed as an outpatient procedure under local anesthesia. Other potential benefits include reduced pain, shorter recovery time, fewer complications, and reduced cost.

Significant research into transcervical methods of sterilization began in the 1970's. Research into several methods continues to the present day. Several of the most significant attempts to develop a safe and acceptable method for transcervical sterilization are discussed below.

Beginning in 1970, several studies were performed involving the blind, transcervical delivery of quinacrine, a sclerosing agent, to the uterus.[22] The quinacrine causes damage to the intramural portions of the fallopian tubes. The damage is sufficiently severe to result in permanent scarring of the fallopian tubes in a high percentage of women. Quinacrine had been delivered transcervically both as a slurry and in pellet form. The most common, recent method of female sterilization with quinancrine involves two transcervical insertions of quinacrine pellets approximately one month apart.[22] Preliminary results of Chilean studies of quinacrine show a 5-year cumulative pregnancy rate of approximately 9 per 100 women for women under age 35 and 3.4 per 100 women for women over age 35.[11] Quinacrine is still being studied for female sterilization (primarily in developing countries).[11] Concerns regarding safety, e.g. mutagencity and carcinogenicity, and efficacy have limited the acceptance of quinacrine.[11,22]

Quinones, et al, began investigating hysteroscopic sterilization with electrocoagulation using monopolar radiofrequency current in 1972.[17] The method used by Quinones involved fluid distention of the uterus, transcervical delivery of a unipolar electrode, and the application of coagulating radiofrequency current.[17] The electrocoagulation was intended to affect occlusion of the tube through tissue scarring which followed this extensive thermal injury. The parameters for the

radiofrequency current were approximately 25 Watts for 4 to 8 seconds.[18] In a study of 800 patients, Quinones reported no complications due to anesthesia, distention fluid, or the radiofrequency current.[18] However, the annual pregnancy rate for the Quinones study was 8.4%.[18] Quinones sited several factors which contributed to the failure rate: procedures were not all coordinated with regard to time of menstrual cycle, investigators were not all proficient in hysteroscopy, and duration of radiofrequency current application was insufficient.[18] In addition to pregnancy complications, Quinones reported one uterine perforation ascribed to investigator lack of experience and one death which may have been caused by bowel damage during radiofrequency current application.[18] Adiana believes that high levels of energy delivery into the fallopian tube, and the subsequent creation of scar tissue, will not result in long-term occlusion.

In the 1980's, transcervical sterilization was attempted using a hydrogelic occlusive device.[3] This implanted device, call the P-block, was studied over a period of ten years and included over 900 woman years of experience.[3] The P-block technique involved distention of the uterus and hysteroscopic delivery of the implanted device (via forceps, and later, a delivery catheter).[3] The hydrogelic body of the P-block device swelled after placement to fill the fallopian tube.[3] The P-block device also featured "retention wings" to prevent its expulsion. Brundin reported that, over time, fibroblastic and vascular ingrowth could occur into the porous surface of P-block device.[3] Studies reported by Brundin indicated that pregnancies occurred due to P-block expulsion (4.6 per 100 woman years) and that some pregnancies occurred despite bilateral retention of the implanted devices.[3] Brundin reported a very low rate of complications, e.g. bleeding, associated with the use of the P-block device.[3] Only one ectopic pregnancy was observed in the studies conducted. Despite significant issues with the performance of the device, there was a high rate of patient satisfaction with the P-block contraceptive method as reported by Brundin.[3]

In the early 1980's, Neuwirth et al, reported on studies involving the transcervical delivery of a tissue adhesive to occlude the fallopian tubes.[15] Methyl cyanoacrylate (MCA) was injected into the fallopian tubes using an intrauterine balloon to drive the adhesive into the isthmic portion of the tubes.[15] The MCA caused inflammation, necrosis, and fibrosis in the fallopian tube over time which was intended to occlude the fallopian tubes.[15] Neuwirth reported on single treatments (single injection) and a two-injection sequence in which a 30-day interval passed in between treatments.[15] Using hysterosalpingography, Neuwirth observed 75% bilateral occlusion in the single treatment cases and 87% bilateral occlusion in the two-treament cases.[15] Neuwirth reported 23 confirmed pregnancies in the 1,083 women treated with MCA.[15] The observed pregnancy rate was approximately 1 per 100 woman years.[14] As reported by Neuwirth, no pregnancies occurred after 6 months of follow-up and no ectopic pregnancies were observed.[15] During the studies, a complication rate of approximately 1% involving hospitalization for symptoms compatible with pelvic inflammation was observed.[15] The need for

multiple treatments and the limited efficacy rate reported were among the limitations of this method.

In studies which continued into the 1990's, a silastic tubal plug was investigated to achieve female sterilization.[25] The treatment involved the hysteroscopic approach to the fallopian tubes, distention of the uterus, and delivery of catalyzed liquid siloxane rubber to each fallopian tube via a catheter.[25] The fluid was allowed to flow to the oviduct, thereby forming a tubal cast which was smallest at the isthmic portion of the tube and larger at either end.[19] The solid silastic cast was intended to achieve sterilization by forming a mechanical occlusion of the tube.[25] (It is important to note that unlike the Adiana treatment, in which the implant is intended to provide a scaffold for a biological block, the solid silicone was intended to form a silicone plug.) van der Leij reported that proper plug implantation was achieved in 82.7% of patients.[25] In the remainder of patients with proper plug implantation, 3.6% were advised by investigators to not rely on the plugs for contraception because of uncertain status, e.g. damaged plug.[25] A total of 324 patients were allowed to rely on the silastic plugs for sterilization.[25] In this group, the pregnancy rate was approximately 2.3% which included one ectopic pregnancy.[25] Also, there were seventeen additional device-related terminations, nine expulsions and eight removals.[25]

More recently, Kerin, et al, have reported on the use of a metal and Dacron coil placed partially into the fallopian tube. [10] This device creates an inflammatory response which, over time, alters the normal tubal architecture and leads to occlusion and pregnancy prevention. This device, approved in 2002 by FDA, is currently marketed as the Essure PBC system. Data from the SS&E show a first year pregnancy prevention rate of 99.4% (95% CI) in the pivotal trial for this product. Also reported was a failure to achieve bilateral placement in 14% of first attempts. Additionally, device expulsions, perforations and failure to achieve satisfactory device location were reported in 4.6% of patients.[53] (See Appendix 11) In addition, this device is much larger than other implants, such as the technique proposed herein, and it is unknown to what extent size and the use of a metal implant will be accepted by patients and clinicians since the use of metal implants precludes certain electrosurgical procedures.

On the basis of this prior work, Adiana began development in 1997 of a new technique for sterilization that would overcome some of the demonstrated shortcoming of prior attempts, as discussed above. The criteria identified in this development work included:

- Delivery of the device should be achievable without extraordinary training or effort for the physician, and without discomfort or risk to the patient.
- Successful placement should be accomplished in a large proportion of patients attempted.
- The device must result in occlusion of the fallopian tube.

- The device must lead to a stable tissue response which is indicative of long term efficacy.

The Adiana treatment involves: 1) hysteroscopic, transcervical introduction of a catheter, 2) hysteroscopically controlled insertion of the distal tip of the catheter device into the fallopian tube lumen, 3) bipolar radiofrequency current application to the tubal lumen, and 4) implantation of a biomaterial matrix in the region of the radiofrequency lesion within the fallopian tube, and 5) in-growth of healthy tissue into the implant, and incorporation of the implant, to create a long-term blockage.

The underlying mechanism proposed by Adiana consists of the following components: The radiofrequency current destroys the epithelial lining of the fallopian tube lumen, and stimulates a wound healing response. The matrix has been designed to provide a suitable architecture for tissue in-growth during this wound healing response. The wound healing response into this unique tissue scaffold results in a complete integration of healthy tissue into the implant. The action of the matrix is not simply to mechanically occlude the tube, but rather to create a tissue scaffold leading to occlusion through the natural healing response.

I. F. KEY TO TERMS

1.5. Key To Terms

AAMI	-	Association for the Advancement of Medical Instrumentation
AC	-	Alternating current
ANSI	-	American National Standards Institute
ASTM	-	American Society for Testing and Measurement
BF	-	Body Floating
BOM	-	Bill of Materials
CA	-	Corrective Action
CAPA	-	Corrective and Preventive Action
CAR	-	Corrective Action Report
CCFL	-	Cold Cathode Fluorescent (backlight)
CCP	-	Cyclic Contraceptive Preparation
CIN	-	Cervical Intraepithelial Neoplasia
CISPR	-	Comité International Spécial des Perturbations Radioélectriques
CPU	-	Central processing unit
CS	-	Component Specification
DB-9	-	A standard 9-pin connector
DC	-	Direct Current
DIUF	-	Deionized Ultrafiltered
DMR	-	Device master record
DOE	-	Design of Experiment
EC or CE	-	European Community
ECO	-	Engineering Change Order
EN	-	Euronorm
EMC	-	Electromagnetic compatibility
ERP	-	Enterprise Resource Planning
EQ	-	Equipment Qualification
FA	-	Final Assembly
FM	-	Form
FMEA	-	Failure Mode Effects Analysis
H&E	-	Haematoxylin and Eosin Stain
HSG	-	Hysterosalpingogram (an -X- ray test that examines the inside of the uterus and fallopian tubes
ID/OD	-	Inner Diameter / Outer Diameter
IEC	-	International Electrotechnical Commission
IFU	-	Instructions For Use
I/O	-	Input/Output
IQ/OQ	-	Installation Qualification/Operations Qualification
ITS-90	-	International Temperature Scale of 1990
LCD	-	Liquid Crystal Display
[redacted]	-	Descriptive name for shape of tubing prior to bonding to distal tip
LED	-	Light Emitting Diode
LHR	-	Lot History Record
[redacted]	-	Matrix Exit Hole. Refers to the shape prior to heat forming

MP	-	Manufacturing Procedure
NBT	-	Nitroblue Tetrazolium (stain)
OC	-	Oral Contraceptive
OCT	-	Optically Clear Tissue Compound
PDA	-	Position Detection Array
PID	-	Proportional, Integral, Differential control algorithm
PL	-	Product Labeling
POST	-	Power On – Self Test
PR	-	Product Routing
PQ	-	Process Qualification
PS	-	Product Specification
PTFE	-	Polytetrafluoroethylene
QI	-	Quality Improvement
QM	-	Quality Manual
RAM	-	Random Access Memory
RFG	-	Radio Frequency Generator
RF	-	Radio Frequency
ROM	-	Read-only Memory
RS-232	-	A serial communications standard
RTID	-	Resistance/Thermocouple/Identification Resistor
SA	-	Sub Assembly
SIN	-	Salpingitis Isthmica Nodosa
SPC	-	Statistical Process Control
SP	-	Standard Procedure
SS&E	-	Summary of Safety and Effectiveness
STD	-	Sexually Transmitted Disease
STN	-	Super twist nematic (display)
TC	-	Thermocouple
TEM	-	Tissue Equivalent Material
TM	-	Test Method
TR	-	Test Report
UL	_	Underwriter's Laboratory
TVUS	-	Transvaginal Ultrasound
UTJ	-	Utero Tubal Junction
WI	-	Work Instruction

I. G. DECLARATION OF CONFORMANCE TO STANDARDS

1.6. Declaration of Conformance To Standards

1.6.1 External Standards

There are no published performance standards for the Adaina Transcervical Sterilization System. The Adiana Generator does conform with recognized standards for electromedical equipment.

Adana product design, manufacture, and testing have been conducted to meet the requirements of:

Title 21 of the Code of Federal Regulations 800 Series

ISO 13485 Quality Systems – Medical Devices – Particular Requirements for the Application of ISO 9001

ISO 10555-1 General Requirements for Sterile, Single use Intravascular Catheters

ISO 10993: 1997 International Standard for Biological Evaluation of Medical Devices, Part 1: Guidance on Selection of Tests

ISO 10993-2:1992: Biological Evaluation of Animal Devices – Part 2, Animal Welfare Requirements

Device Evaluation General Program Memorandum #G95-1, Use of International Standard ISO-10993; Biological Evaluation of Medical Devices Part 1: Evaluation and Testing, May 1, 1995.

ANSI/AAMI/ISO 11134:1993 Requirements for validation and routine control-industrial moist heat sterilization

ASTM D416-99 (1999) Standard Practice for Performance Testing of Shipping Containers and Systems. The RF Generator is designed to pass tests based on representative shipping conditions as defined by Adiana.

UL 60601-1 (2003): (IDE [1997]) Medical Electrical Equipment: General Requirements for Safety

IEC 601-1 (1988): Amendment 1, 1991; Amendment 2, 1995): Medical electrical equipment, Part 1: General requirements for safety. The RF Generator is designed to meet or exceed the Body Floating (BF) patient isolation rating.

IEC 601-1-2 (1993) Medical Electrical Equipment, Part 1: General requirements for safety. 2. Collateral Standard: Electromagnetic Compatibility – Requirements and Test

IEC 601-1-2 (2001) + A1 (Original Device - 1993) (Emissions and Immunity)

IEC 601-1-4 (1996): +A1:1999 Medical electrical equipment, Part 1-4: General requirements for safety. Collateral Standard: Programmable Electrical Medical Systems

IEC 601-2-2 (1998): Medical electrical equipment, Part 2: Particular requirements for the safety of high frequency surgical equipment

IEC 606-1-1 (2003): (IDE 1992: Amendment 1, 1995) Medical Electrical equipment, Part 1: General requirements for safety. 1. Collateral Standard: Safety Requirements for Medical Electrical Systems

ANSI/AAMI HF 18:2001 Section 4.2.5.1 (Dielectric withstand, 60 Hz), Section 4.2.5.2 (High frequency leakage current), and 4.2.5.4 (Dielectric withstand of Accessories); European EMC Directive 89/336/EEC and Medical Directive 2004/108/EC

1.6.2 Internal Product Specifications

In addition, Adiana has developed internal product specifications for both the Adiana RF Generator and the Adiana Delivery Catheter with Matrix. These documented product specifications are included in Appendices 2-4.

I. H. OVERVIEW OF PRIOR STUDIES

1.3.5 Executive Summary: Summary of Information Contained in Module 4

Executive Summary Table of Contents:

Prior Studies

Clinical Report

Financial Disclosure Information

Labeling

Training

EASE Post Approval Study

Executive Summary: Prior Clinical Studies

1) Access Studies

The ability of the Adiana Delivery Catheter to access the intramural portion of the fallopian tube was evaluated as a component of all Peri-Hysterectomy and Pre-Hysterectomy studies. Combined device performance over a total of 369 tubal access attempts yielded 336 successful placements (91%). This pooled analysis includes several versions of the Adiana Delivery Catheter.

Adiana also performed a study specifically analyzing only catheter access in a patient population reasonably close to the intended target population. The results were to be indicative of the expected catheter performance in the EASE investigational study.

The Healthy Patient Access Studies recruited a total of 43 patients who were seeking elective tubal ligation. Immediately prior to a scheduled laparoscopic tubal ligation, the Adiana Procedure was performed except there was no RF energy delivery and no Matrix delivery. The endpoint of the study was simply to determine that the Delivery Catheter was placed at the correct position in the fallopian tube based on visual observation and that the PDA contact was satisfied on the Adiana RF Generator. Access rates ranged from 91% for the original handle to 100% for the current handle.

2) Peri-Hysterectomy studies

After verification of device performance through bench, *in vitro* and animal testing, evaluation in human clinical studies was undertaken in a step-wise fashion. In total, 128 patients were treated in a series of peri-hysterectomy studies. The studies were performed in pre-menopausal women scheduled to undergo elective hysterectomy. Immediately prior to the hysterectomy, treatment with the Adiana System was performed. Histology evaluation evaluated uniformity and completeness of epithelial destruction, depth and uniformity of the thermal lesion, tubal lesion length, and position of the Matrix within the lesion.

The study was separated into two stages. The first stage involved the investigation of how varying temperature/time parameters and electrode length/diameters dimensions impacted lesion creation and serosal temperature rises. This allowed the selection of one temperature/time and electrode configuration that safely creates an acceptable lesion.

The second stage involved verification testing of the selected temperature setting. It was demonstrated at this setting that lesions could be generated reproducibly,

that treatment with the Delivery Catheter caused no risk to adjacent organs or structures, and that Matrix delivery was reliably obtained. In addition, studies evaluating device modifications were performed.

During the course of all Peri-hysterectomy studies, there were no patient complications or adverse clinical events due to either the Adiana System or Procedure.

3) Pre-Hysterectomy Studies

After successful completion of animal fertility studies and human Peri-Hysterectomy studies, Adiana undertook a series of clinical studies to determine the ability of the Adiana System to occlude fallopian tubes in patients.

The Pre-Hysterectomy protocol [redacted] was designed to evaluate the Adiana System with regard to safety and efficacy in the human anatomy. The Pre-Hysterectomy studies are organized into a series of "Pilot-Pre" studies (23 patients) and a single "Pivotal-Pre" study (42 patients). The Pilot-Pre studies were a series of implant studies designed to gain information relating to lesion parameters, Matrix configurations and/or device designs to optimize the treatment. Once confidence was obtained that the treatment had been optimized and the ingrowth period defined, the Pivotal-Pre study was conducted to confirm the results with a greater number of subjects.

The Pilot-Pre series examined two different Matrix configurations, and two different ingrowth periods. There were also changes in manufacturing methods during these studies. Several major conclusions were drawn from in the Pilot Pre-Hysterectomy Studies:

- The access rate in this population was high, with 84.1% of attempted tubes successfully accessed.
- Patients were comfortable with the Matrix during the period following implantation.
- When properly placed, the Matrix was retained during the period following implantation.
- Tubal occlusion was demonstrated by utilizing:
  - Treatment parameters of 64°C/60 seconds
  - Standard Matrix [redacted]
  - 12 week ingrowth period
  - Steam Sterilization
- Tissue ingrowth (at the temperature-time parameters and device configuration described above) was found to be space filling and to consist of cell types which would lead to stable, long term occlusive ingrowth.
- There were no adverse events during this study.

The subsequent Pivotal Pre-Hysterectomy Study utilized one Matrix design, one ingrowth period and one basic Delivery Catheter configuration. Specific findings in this study included:

- Blood vessels were found to be abundant in the wall of the fallopian tube and within the ingrowth. The counts of blood vessels within the Matrix indicate that it is well vascularized and consistent with healthy tissue. These vessels were found to penetrate into the deeper pores of the Matrix so that the entire Matrix was well supplied.

- The removal of the surface epithelium was consistently accomplished in the tubes from this study. This is regarded as an indication of the effectiveness of the lesion and demonstrates that the lesion parameters were appropriate.

- Inflammation was generally mild with a sprinkling of lymphocytes. There was a general absence of lymphocytic foci and the level of lymphocytes was consistent with the normal background level found in the fallopian tube. There were only moderate amounts of macrophages, PMNs, and few eosinophils and plasma cells were observed. These observations indicate that the implant was fairly benign. The absence of large numbers of giant cells is also taken as a measure that a foreign body response was not evoked.

- There were very few layers of fibrosis surrounding the Matrix, which indicates a fibrotic capsule or scar tissue had not formed. This is also an indication that the lesion was sufficient to direct the repair mechanism toward tissue ingrowth rather than walling off. Only small amounts of necrosis were observed within the ingrowth which is another indication that the tissue is viable and stable. The mean score for necrosis is at the level of none to slight amounts, which is probably a result of the abundant vascular supply.

Adverse Events - There were no clinically significant adverse events during the course of this study.

I. I. OVERVIEW OF PIVOTAL CLINICAL TRIAL

Executive Summary: Clinical Report

Purpose of the Study

A pivotal clinical trial (called the "EASE" trial) was conducted to demonstrate the safety and effectiveness of the Adiana System in providing permanent contraception. The EASE clinical trial was a prospective, single-armed, multi-center, international trial that was conducted in the U.S., Australia, and Mexico. The targeted study population was 400 women in whom bilateral Matrix placement was achieved. The study used findings from the U.S. Collaborative Review of Sterilization (CREST study) as a qualitative benchmark.

Study Endpoints and Design

Primary efficacy endpoint for the clinical trial:

- Pregnancy prevention rate after 12 months of reliance on the Adiana System

Secondary endpoints of the clinical trial included:

- 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

The EASE clinical trial had two phases: 1) the Waiting Period after initial Adiana System treatment and, 2) the Wearing Follow-Up Period post tubal occlusion. 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. If the HSG evaluation was satisfactory, 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 was not satisfactory, then, depending on the circumstances, women were given the option to wait an additional 3 months for a second HSG to see if blockage would occur, or, seek alternative contraception. 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. Additionally, 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 Visits

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. 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. These 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
- adverse events or unusual symptoms.

Effectiveness Results

Placement Rates

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 Rates
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.

Pregnancy Prevention Effectiveness
Of the 570 women relying on the Adiana System for pregnancy prevention, all have been followed for 12 months; 321 have been followed for 24 months; and 133 have been followed for 36 months. During the one-year follow-up period, there were six pregnancies: three were attributable to physician error (misinterpretation of HSG results) and the remaining three were due to method failure. During the two-year follow-up period, there were three pregnancies attributable to method failure. Table 1.2 presents the principle contraceptive effectiveness rates for the EASE clinical trial, as of March 1, 2007.

Table 1.2: Effectiveness Results as of March 1, 2007

Cumulative Failure Rates	Method Failures	All Pregnancies
One-Year*	0.54% (95% CI 0 to 1.05%)	1.08% (95% CI 0-1.80%)
Two-Year*	1.29% (95% CI 0 to 2.17%)	1.82% (95% CI 0 to 2.84%)
Three-Year*	1.29% (95% CI 0 to 2.17%)	1.82% (95% CI 0 to 2.84%)

*The one-, two-, and three-year effectiveness rates for the Adiana System are comparable to the effectiveness rate for other methods of tubal sterilization at these time points; however, the two and three year data are incomplete and these rates may change as further data are obtained. Follow-up of the women in the EASE trial is ongoing, and will continue to 5 years of follow-up. As updated data regarding longer-term failure rates are available, it will be included in the product labeling.

Patient Demographics for the EASE trial

The patient population of the EASE trial consisted of 645 women in whom treatment was attempted. All study participants were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had been pregnant at least once, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following Matrix placement. Table 1.3 presents age distribution and other patient demographics

Table 1.3: Age Distribution and Patient Demographics (N=645)

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)

Other Results from the EASE Trial

Adverse Event Rates

Table 1.4 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 1.4: Side effects reported on day of placement procedure (N=653 procedures)

Event	Percent
Cramping	25%
Vaginal Spotting	24%
Post-procedural Bleeding	10%
Pelvic Pain	9%
Nausea	6%
Back Pain	6%
Headache	4%
Post-procedural Pain	2%
Vaginal Discharge	2%
Dysuria	2%
Vomiting	2%
*Other	2%

*Includes events that occurred at a rate >0.5% and ≤1%: abdominal distension, arthralgia, post-procedural discomfort, and vasovagal reaction.

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.

Table 1.5 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 approx. 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, but were rated by the Investigator as at least "possibly" related to the Adiana System were cramping unrelated to menses (6%), dysmenorrhea (5%) and vaginal bleeding(4%) All other events occurred in less than 3% of women.

Table 1.5: Adverse Events by Body Systems, First Year of Reliance[1,2] (N=625 patients implanted with at 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

During the first year of reliance on the Adiana System, one patient experienced an isthmic ectopic pregnancy, which was successfully resolved by treatment with medication.

Patient Satisfaction/Comfort
Women in the EASE trial consistently rated their overall satisfaction and comfort in wearing the Adiana matrices as very high. More than 98% of patients reported that they tolerated the Adiana Procedure "well" to "excellent". The majority of women returned to normal activities within one day or less after the procedure. At all study visits after the One-Week visit, more than 99% of women rated their comfort with wearing the Adiana matrices as "good" to "excellent". At all study visits, at least 96% of women rated their overall satisfaction as somewhat to very satisfied (this included women who were not able to rely on the Adiana matrices). No patients reported wearing of the device as "intolerable". There were no requests for Matrix removal due to discomfort.

Non-Relying Pregnancies
There were 5 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 Matrix following unsuccessful treatment). None of these 5 women became pregnant while relying on the Adiana matrices for contraception. Four of these pregnancies resulted in normal term deliveries, and one was electively terminated.

I. J. FINANCIAL DISCLOSURE INFORMATION

Executive Summary: Financial Disclosure Information

Adiana Inc. was a private company and the original sponsor for IDE G020172 for the Adiana Transcervical Sterilization System. The first patients were treated under this IDE in 2002. Subsequently a Modular PMA shell was undertaken [redacted]. Adiana was acquired by Cytyc Corporation on March 16, 2007.

Pursuant to 21 CFR 54, 812, and 814, the Sponsor of a Premarket Application is required to disclose any financial conflict of interest by any investigator who supplies data supporting the safety or effectiveness of a product. (Forms 3454 and 3455 are included in Appendix 9). The Financial Disclosure section contains summaries of the following categories:

- Financial Arrangements
- Significant other payments
- Proprietary interest
- Significant equity interest

Due to the change in company ownership during the course of the study of the Adiana Transcervical Sterilization system, two disclosures are provided, one for Adiana and one for Cytyc.

I. K. OVERVIEW OF PROPOSED LABELING

Executive Summary: Labeling

A variety of labeling components will accompany the Adiana Transcervical Sterilization System. There are two principal components of the system, the Adiana Delivery Catheter and the Adiana RF Generator. Labeling has been organized into the following categories:

Adiana Delivery Catheter Applied Labeling
- Pigtail Serial Number Tag
- Pouch and Box Label
- Catheter Cable Label

Adiana RF Generator Applied Labeling
- Front and rear panel labels
- Software display screens

System Labeling (may be provided within packaging or separately available)
- Draft Summary of Safety and Effectiveness
- Draft System Instructions for Use
- Draft RFG Specification and Installation Manual
- Draft HSG Protocol
- Draft Patient Brochure

A table describing each of the labeling components is provided. Samples of applied labeling and drafts of accompanying labeling are attached in Appendices 10-16. Pictures of silk-screened labeling are provided.

The RF Generator utilizes a software menu driven display to guide the user through the various steps of the Adiana Procedure. As the RF Generator transitions from one mode to the next it continuously checks for errors in the Delivery Catheter, as well as within the RF Generator itself. These screens are also overviewed in the labeling section and explained in detail in the RF Generator Specification and Installation Manual.

System labeling consists entirely of Draft versions to be completed upon finalization of the Summary of Safety and Effectiveness, and further discussions with FDA.

I. L. OVERVIEW OF PROPOSED TRAINING

Executive Summary: Training

The Module 4 Training Section contains descriptions of the design and delivery of physician training for both the EASE clinical study and for proposed commercial training. During the EASE study, Cytyc provided training for two "tiers" of investigators: the first group was the initial investigators who joined the study when it began in October 2002, and the second group consisted of investigators who joined when the study expanded in September 2003. By responding to investigator feedback, Cytyc was able to improve the quality of training from the first group to the next.

EASE investigator training included didactic presentations, hands-on practice with hysteroscopic simulators, and actual clinical experience with clinical trainers. Didactic material was collected and organized into modules that would assist in the comprehension of defined learning objectives. Whenever possible, video and live demonstrations were also provided, and a hysteroscopic simulator was utilized to provide hands-on practice before proceeding to clinic. Additionally, all investigators received training in the RF Generator and Delivery Catheter Instructions for Use.

The physician training program for commercialized product has been developed utilizing feedback acquired through two tiers of EASE clinical study investigator training, and current transcervical sterilization training practice in the marketplace. It is Cytyc's intention to provide a complete training program for all physicians who require it.

Once product is commercialized, Cytyc will market devices exclusively to physicians who have successfully completed the training program. To be eligible for Adiana Procedure training, physicians shall be certified in the field of gynecology by a national organization (for example, the American College of Obstetrics and Gynecology in the USA) or be qualified for certification, and shall be experienced in the use of operative hysteroscopy at the physician's primary clinical facility. Physicians who have not yet achieved competency in hysteroscopy will need to obtain training externally. Cytyc will generate and provide a list of resources for training in hysteroscopy.

In order to reach an optimal balance between providing ample background information and customized training aimed at the correct learning level, Cytyc will deliver training that targets two different physician experience levels:

1) Track One will be offered to hysteroscopists already performing transcervical sterilization, and
2) Track Two will address experienced hysteroscopists (defined as those who have operative hysteroscopy privileges at their clinical facility).

Physicians who are not competent hysteroscopists will not be eligible to procure the Adiana System and will not be trained in Adiana technique.

All physicians will receive didactic training and hysteroscopic simulation training. A draft Physician's Training Manual based on the PowerPoint presentation for the didactic portion can be found in the appendices. It will be provided to all physicians who participate in the Adiana training program. While Track One physicians who are already competent with transcervical sterilization will have the option of arranging for case preceptorship, it will be required for Track Two physicians. Cytyc clinician trainers will maintain a training record and checklist of completed physician training activities. Product will be provided only to physicians who complete the appropriate training program.

Performing and accurately interpreting HSGs has been an important aspect of the Adiana Training Program for the EASE Clinical Study and continues to be for commercialized product. To ensure that physicians who interpret HSGs for commercial product are successful, a separate training program has been developed. Designed for both gynecologists and radiologists, it will present information specific to performing the Adiana procedure, interpreting Adiana HSGs and managing challenging cases. A separate HSG Manual has been drafted along with PowerPoint slides.

I. M. SUMMARY OF PROPOSED POST APPROVAL STUDY

Executive Summary: Post Approval Studies

The EASE study was designed with a one year primary endpoint, and will follow all patients out to 5 years of reliance.

Per Regulatory Guidances, *"Procedures for Handling Post-Approval Studies Imposed by PMA Order"* issued December 21, 2006 and *"Guidance for Industry and Staff – Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act,"* issued on April 25, 2006, Cytyc will research through the continuation of the EASE Clinical Study:

What are the 3, 4, and 5 year device failure/effectiveness rates?

Cytyc will continue the current study per IDE G020172 with yearly follow-up reporting out to 5 years.

II. DRAFT SUMMARY OF SAFETY AND EFFECTIVENESS

DRAFT PREPARED BY CYTYC;
NOT YET REVIEWED BY FDA

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: Contraceptive Tubal Occlusion Device and Delivery System

Device Trade Name: Adiana Transcervical Sterilization System

Applicant's Name and Address: Cytyc Corporation
250 Campus Drive
Marlborough, MA 01752

Premarket Approval Application (PMA) Number: (P070022)

Date of Panel Recommendation:

Date of Notice of Approval to Applicant:

II. 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.

III. Contraindications

The Adiana Transcervical Sterilization System should not be used in patients who:

- Are uncertain about their desire to end fertility
- Have presence of gross genital infection, or sepsis
- Have intra-uterine pathology which would prevent access to the tubal ostium and intramural portion of the fallopian tube, such as large submucous fibroids or uterine adhesions
- Are currently taking immunosuppressive medications
- Are pregnant or have suspected pregnancy
- Have had uterine perforation within the last 3 months
- Are currently less than three months since their last delivery or abortion

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

IV. Warnings and Precautions:

A list of Warnings and Precautions can be found in the device labeling.

V. Device Description

The Adiana Transcervical Sterilization System (Adiana System) provides for female sterilization by occlusion of the fallopian tubes via a hysteroscopic transcervical approach.

A. Adiana Transcervical Sterilization System Components

The Adiana Transcervical Sterilization System is comprised of the following components:

- Delivery Catheter with split Introducer
- Matrix
- Radiofrequency (RF) Generator

Delivery Catheter

The Delivery Catheter consists of a multi-pin connector which is attached to the handle by an 18 inch cable, a plastic handle with matrix-release mechanism and a 40.5 cm catheter shaft. The catheter shaft contains conductors for the thermocouples, RF current-conducting wires, and a matrix-release mechanism. The distal portion of the catheter has four electrodes, two embedded thermocouples and a Position Detector Array (PDA). The Delivery Catheter contains a push button release mechanism which, once triggered by the operator, will automatically release the Matrix with no further action required from the operator. The device is supplied sterile, and is a single use device. The Delivery Catheter is packaged with the split Introducer, which is an accessory to assist in placing the catheter into the operating channel of the hysteroscope. A photograph of the Delivery Catheter is included below in Figure 1.

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

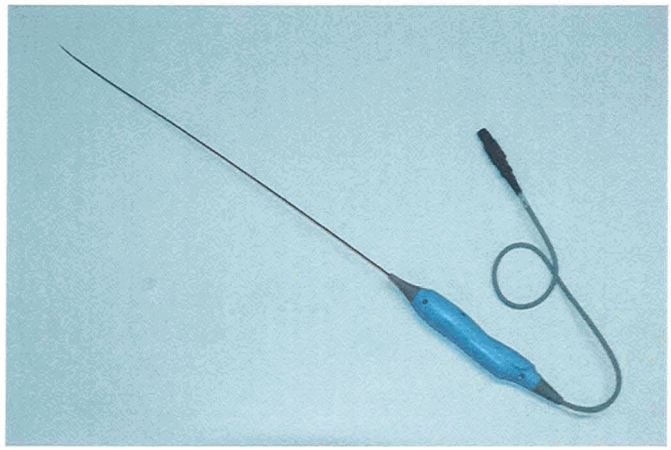
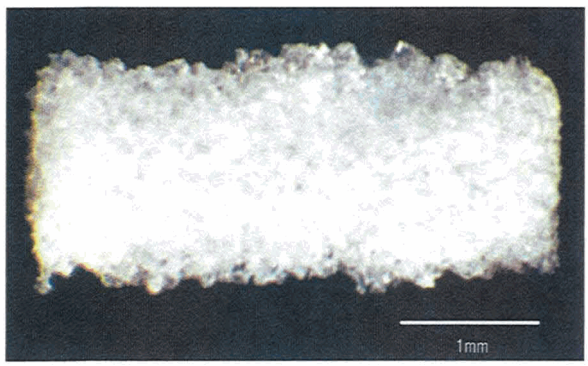
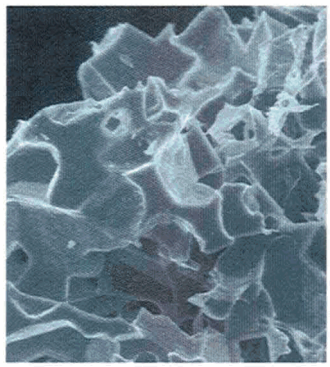


Figure 1: Delivery Catheter

Matrix

The non-absorbable biomaterial 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 material utilized has a long history of implant applications, and therefore, has a large body of safety information as well as biomaterial testing data. In addition, longer term implant data in animals and humans have shown no adverse tissue effects, with only mild localized responses. The Matrix is shown in Figures 2a and 2b.





2a **2b**

Figure 2a: Entire Matrix side view
Figure 2b: Close-up view of Matrix showing random architecture of pores

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

Radiofrequency (RF) Generator

The Radio Frequency Generator (or "RF Generator") is custom designed for the Adiana procedure. There are no user-selectable settings for power, energy or time. All treatment parameters are automatically controlled. The RF Generator has a LCD front panel display which prompts the operator through the sequence of steps to complete a procedure. It includes accessories: a foot switch for control of certain generator functions and a cable to connect the generator to the Delivery Catheter. The RF Generator is shown below in Figure 3.

Figure 3: RF Generator

B. Mechanism of Action

1. Placement

The Matrix is placed in the fallopian tube through hysteroscopic, transcervical introduction of the Delivery Catheter into the transmural portion of the fallopian tube. Low power (<3 Watts) RF energy is applied to the intramural portion of the fallopian tube. This energy generates heat in the fallopian tube tissue creating a superficial thermal lesion. The RF Generator regulates its output power to maintain the desired tissue temperature throughout the lesion formation period (one minute). Following delivery of the RF energy, the Matrix is implanted into the tubal lumen in the region in which the lesion was formed.

2. Tissue In-growth

The Matrix remains implanted within the fallopian tube. Subsequent wound healing leads to tissue occupation of the porous Matrix architecture. The circumferential in-growth through the Matrix results in occlusion of the fallopian tube, which in turn prevents the passage of sperm.

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

3. Permanency of Tubal Occlusion

The clinical data regarding long-term Matrix implantation in the fallopian tube is based on 12-36 months of implantation, and more than 16,000 cumulative months of patient wearing of the implants. Results of histological analysis of explanted matrices from eight patients undergoing elective hysterectomy for medical reasons have indicated the biocompatibility of the implant, the capability to provide total occlusion of the fallopian tube by tissue ingrowth into the pores of the implant, and the presence of a normal foreign body reaction indicating a normal biocompatible implant response implant response at an average implant period of 3.1 years.

VI. Alternative Practices and Procedures

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

- Hysterectomy
- Salpingectomy
- Tubal ligation
- Tubal Fulguration
- Application of clips
- Tubal sterilization implant (metallic), and

The permanent male method is vasectomy.

VII. Marketing History

The Adiana Transcervical Sterilization System has not been marketed in any country.

VIII. Observed and Potential Adverse Effects of the Device on Health

Between November 13, 2002 and April 28, 2005, a total of 645 women underwent an Adiana Procedure in the pivotal EASE clinical trial to evaluate the safety and effectiveness of the Adiana Transcervical Sterilization System. Some women underwent more than one procedure if successful bilateral placement was not achieved in the initial procedure. Overall, bilateral placement success was achieved in 95% of patients in the trial.

DRAFT PREPARED BY CYTYC; NOT YET REVIEWED BY FDA

A. Observed Adverse Events

Table 1 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 1: Side effects 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.
*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.

Table 2 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 approx. 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, but were rated by the Investigator as at least "possibly" related to the Adiana System were cramping unrelated to menses (6%), dysmenorrhea (5%) and vaginal bleeding(4%) All other events occurred in less than 3% of women.

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Table 2: Adverse Events by Body Systems, First Year of Reliance[1,2] (N=625 patients implanted with at 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

During the first year of reliance on the Adiana System, one patient experienced an isthmic ectopic pregnancy, which was successfully resolved by treatment with medication.

B. Potential Adverse Events Not Observed in Clinical Studies

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; and

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- 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.

IX. Summary of Preclinical Studies

A. Laboratory Studies

1. Concept / Feasibility Testing

An extensive series of investigations was performed to characterize the safety of the Adiana procedure, to determine the proper device configuration and to define a clinical protocol. This research focused on all aspects of device design and performance, including optimal access to the fallopian tube, RF lesion creation, Matrix delivery, host tissue response and in-growth, tubal occlusion and pregnancy prevention.

Mulitple *in vitro* studies were performed utilizing extirpated uteri from patients undergoing elective hysterectomy. Following removal, the uteri were used to evaluate catheter handling and performance. In addition, the ability to deliver RF energy and create a superficial thermal lesion within the fallopian tube was evaluated. Histological analysis following treatment in extirpated uteri samples was used to define proper RF treatment parameters.

In vitro studies demonstrated that the lesion created by RF was shallow and caused no serosal temperature rise. Lesion creation was uniform and reproducible, and Matrix delivery was shown to be feasible.

2. Verification Testing

Engineering / Bench testing of the Adiana System has been conducted in order to verify that the design output conforms to the design input requirements described in the product specification. The testing protocol 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
- Matrix Inspection

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- Electrode Tensile
- Rotational Turns to Failure
- Electrode Sheath / Polyimide Junction Tensile
- Proximal Sheath Ring Bond Tensile
- Catheter Shaft to Strain Relief Tensile
- Push Rod Crimp Joint Tensile
- Push Rod to Chassis Tensile

All results obtained during this evaluation were acceptable. The results verify that the design output conforms to the design input requirements described in the product specification.

Additionally, electrical safety and bench testing were performed on the RF Generator. All product design activities were performed in accordance with written product development procedures and in compliance with ISO 13485. Certification of Compliance and documentation of successful test results for the RF Generator were achieved.

RF Generator verification testing was conducted on RF Generator assemblies to verify that all requirements specified in the hardware requirement specification were met. Testing included the following:

- AC Mains Configuration Test
- Indicators and Audible Beep
- RF Waveform Test
- Output Voltage and Current Range Test
- RF Measurement Accuracy
- Temperature Measurement Accuracy
- PDA Measurement
- Electrical Safety
- High Frequency Leakage Test
- Defibrillator-Proof Test
- Clock Accuracy
- EMC Test
- Dimensions and Weight
- Temperature Measurement Range
- Clock Battery Life
- PDA Operation during RF Output
- Power to Catheter ID Resistor
- Resistance to Cleaning Solutions
- Operation at 50 Hz line Frequency

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All results obtained during this evaluation were acceptable. Additionally, RF Generator Software Verification and Validation testing was performed. All software verification and validation test results met the desired criteria.

3. Biocompatibility

Material Safety Testing of the Delivery Catheter and Matrix was performed to ensure that raw materials, manufacturing, and sterilization processes have resulted in a biocompatible product. The Delivery Catheter is considered a "Surface Contact" device that contacts breached or compromised surfaces (the interior of the fallopian tube is considered to be "compromised" following lesion formation) with contact duration less than 24 hours. This testing also meets testing guidelines for limited duration contact with mucosal surfaces. The Matrix, delivered by the Delivery Catheter, is an "Implant Device", which contacts tissue, with permanent contact duration.

The implanted component, the Matrix, comprised of a fully cured silicone biomaterial, has been tested separately and together with the Delivery Catheter. Additionally, non-carcinogenicity of this material has been established through manufacturer testing, Cytyc bench and animal testing, historical data, and additional information provided by the manufacturer.

Results of the biocompatibility testing demonstrated that the Delivery Catheter and Matrix meet the biocompatibility requirements for cytotoxicity, genotoxicity, irritation, acute systemic toxicity, sensitization, pyrogenicity, and mutagenicity. Testing has demonstrated this product to be compliant with the biocompatibility requirements of ISO 10993-1.

4. Other Animal Studies

There were two different general protocols used in the development of the Adiana System. For these studies the rabbit model was used in the assessment of acute RF performance, tissue in-growth into the Matrix, fallopian tube occlusion and pregnancy prevention.

Short term studies, assessed histologically, were implemented to evaluate ingrowth characteristics and RF lesion creation. Longer term studies, lasting up to 12 months, evaluated the ability to occlude fallopian tubes and prevent pregnancy over long time periods; they included histological analyses and tubal patency testing as well as breeding tests to assess the ability to prevent pregnancy. Studies showed space-filling ingrowth at each time point with tissue fully occupying the pores of the Matrix, leading to tubal occlusion as demonstrated in dye pressure tests. Additionally, histological analysis showed

that implants were well tolerated by the host, with cellular ingrowth that showed low inflammation and no evidence of any fibrous capsule formation.

These animal studies confirmed that the Adiana System results in tubal occlusion as demonstrated by rigorous challenge with pressurized fluid. Additionally, mating studies demonstrated pregnancy prevention at 6 months and 12 months post implant.

B. Sterilization

The Delivery Catheter is for single use and not intended for reuse or resterilization. The Delivery Catheter with Matrix and accessories are packaged in a single tray and are sterilized by steam (moist heat).

Sterilization testing was based on ANSI/AMI/ISO 11134-1993. Sterilization validation testing demonstrated that the moist heat sterilization process utilized for the Delivery Catheter and accessories achieves a Sterility Assurance Level of 10^{-6}.

C. Shelf-Life Testing

Shelf-life testing was conducted on aged products per relevant ASTM and ISO Standards and included performance, seal strength, and sterile barrier testing. 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.

X. Clinical Studies

A. Early Clinical Studies

1) Access Study – 43 patients

This clinical protocol was performed with patients seeking elective tubal ligation. The Delivery Catheter was utilized to access the fallopian tube immediately prior to a scheduled tubal ligation. In this study, no RF energy nor matrix delivery was performed. This study was designed to evaluate the ability of the Delivery Catheter to access the fallopian tube in a patient population which was similar to the target population for this device. The results of this study showed that the Delivery Catheter has a high access rate in a population of patients seeking tubal ligation.

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2) Peri-Hysterectomy Studies – 128 patients

Patients receiving elective hysterectomy were treated with the Adiana System immediately prior to hysterectomy. These studies showed that controlled lesions could be obtained reproducibly, that treatment with the Delivery Catheter caused no risk to adjacent organs or structures, that there was no risk of thermal injury during treatment and that the Matrix delivery was reliably obtained.

3) Pre-Hysterectomy Studies – 65 patients

Pre-Hysterectomy studies involved the treatment of hysterectomy patients 6 to 12 weeks prior to their planned hysterectomy procedure. Multiple device configurations were investigated during the course of several Pilot Studies. Once a final treatment protocol and Matrix configuration were selected, a series of 42 patients were evaluated in the Pivotal Pre-Hysterectomy Studies. The results of these studies showed that the Adiana System occludes the fallopian tube within a period of 12 weeks based on clinical hysterosalpingography (HSG), a rigorous *ex-vivo* pressurized fluid assay ('retrograde salpingography' or RSG) and histological assessment.

Clinical Studies on Safety and Effectiveness

Purpose of the Study

A pivotal clinical trial (called the "EASE" trial) was conducted to demonstrate the safety and effectiveness of the Adiana System in providing permanent contraception. The EASE clinical trial was a prospective, single-armed, multi-center, international trial that was conducted in the U.S., Australia, and Mexico. The targeted study population was 400 women in whom bilateral Matrix placement was achieved. The study used findings from the U.S. Collaborative Review of Sterilization (CREST study) as a qualitative benchmark.

Study Endpoints and Design

Primary efficacy endpoint for the clinical trial:

- Pregnancy prevention rate after 12 months of reliance on the Adiana System

Secondary endpoints of the clinical trial included:

- 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

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The EASE clinical trial had two phases: 1) the Waiting Period after initial Adiana System treatment and, 2) the Wearing Follow-Up Period post tubal occlusion. 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. If the HSG evaluation was satisfactory, 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 was not satisfactory, then, depending on the circumstances, women were given the option to wait an additional 3 months for a second HSG to see if blockage would occur, or, seek alternative contraception. 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. Additionally, 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.

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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 Visits

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. 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. These 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
- adverse events or unusual symptoms.

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Effectiveness Results

Placement Rates

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 Rates

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.

Pregnancy Prevention Effectiveness

Of the 570 women relying on the Adiana System for pregnancy prevention, all have been followed for 12 months; 321 have been followed for 24 months; and 133 have been followed for 36 months. During the one-year follow-up period, there were six pregnancies: three were attributable to physician error (misinterpretation of HSG results) and the remaining three were due to method failure. During the two-year follow-up period, there were three pregnancies attributable to method failure. Table 3 presents the principle contraceptive effectiveness rates for the EASE clinical trial, as of March 1, 2007.

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Table 3: Effectiveness Results as of March 1, 2007

All Pregnancies			
Cumulative Failure Rates	**Effective Sample Size**	**Failure Rate**	**95% Two-Sided CI for Failure Rate**
One-Year*	557.5	1.08%	(0.22%, 1.93%)
Two-Year*	397.0	1.82%	(0.63%, 3.02%)
Three-Year*	168.5	1.82%	(0.63%, 3.02%)
Method Failures			
Cumulative Failure Rates	**Effective Sample Size**	**Failure Rate**	**95% Two-Sided CI for Failure Rate**
One-Year*	554.5	0.54%	(0.00%, 1.15%)
Two-Year*	397.0	1.29%	(0.25%, 2.33%)
Three-Year*	168.5	1.29%	(0.25%, 2.33%)

*95% two-sided confidence intervals derived using life-table methods.
The one-, two-, and three-year effectiveness rates for the Adiana System are comparable to the effectiveness rate for other methods of tubal sterilization at these time points; however, the two and three year data are incomplete and these rates may change as further data are obtained. Follow-up of the women in the EASE trial is ongoing, and will continue to 5 years of follow-up. As updated data regarding longer-term effectiveness rates are available, they will be included in the product labeling.

Patient Demographics for the EASE trial

The patient population of the EASE trial consisted of 645 women in whom treatment was attempted. All study participants were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had been pregnant at least once, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following Matrix placement. Table 4 presents age distribution and other patient demographics

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Table 4: Age Distribution and Patient Demographics (N=645)

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)

Other Results from the EASE Trial

Adverse Event Rate

Adverse events observed in the EASE trial are discussed in Section VIII.

Patient Satisfaction/Comfort

Women in the EASE trial consistently rated their overall satisfaction and comfort in wearing the Adiana matrices as very high. More than 98% of patients reported that they tolerated the Adiana Procedure "well" to "excellent". The majority of women returned to normal activities within one day or less after the procedure. At all study visits after the One-Week visit, more than 99% of women rated their comfort with wearing the Adiana matrices as "good" to "excellent". At all study visits, at least 96% of women rated their overall satisfaction as somewhat to very satisfied (this included women who were not able to rely on the Adiana matrices). No patients reported wearing of the device as "intolerable". There were no requests for Matrix removal due to discomfort.

Non-Relying Pregnancies

There were 5 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 Matrix following unsuccessful treatment). None of these 5 women became pregnant while relying on the Adiana matrices for contraception. Four of these pregnancies resulted in normal term deliveries, and one was electively terminated.

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XI. Conclusions Drawn from Studies

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.

XII. Risk/Benefit Analysis

A. Risks

Risks noted with the Adiana System during the EASE clinical trial included pregnancy and ectopic pregnancy. Although pregnancy events occurred during the clinical trial, the one-, two-, and three-year effectiveness rates for the Adiana System are comparable to the effectiveness rate for other methods of tubal sterilization at these time points. Additionally, the incidence of ectopic pregnancy seen in the EASE clinical trial was less than that reported in the published literature for other tubal sterilization methods.

In addition, some women were not able to rely on the Adiana System for contraception due to either inability to achieve bilateral Matrix placement (5.3%) or inability to achieve bilateral occlusion following bilateral Matrix placement (5.6%).

B. Benefits

The Adiana System provides permanent birth control without invasive surgery or general anesthesia and their associated risks.

The Matrix is a non-metallic implant that is placed solely within the intramural portion of the fallopian tube. There is no foreign body component that extends into the uterus, nor is there persistent uterine or tubal irritation

The Adiana Procedure can be rapidly performed (average duration of approximately 11 minutes in the EASE clinical trial), is highly safe, and well tolerated by patients. During the EASE clinical trial there were no uterine or tubal perforations reported during the Adiana treatment procedures. There were also no reports of aberrant burns, nor other injuries related to the delivery of RF energy and Matrix placement within the fallopian tubes. More than 98% of patients reported that they tolerated the Adiana Procedure "well" to "excellent".

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Wearing of the Adiana matrices is highly safe and well tolerated by patients. The majority of women returned to normal activities within one day or less after the procedure. There have been no reported allergic or adverse reactions to the Matrix, no signs of infection related to the matrices, and no need for any Matrix removals. At all study visits, the vast majority of women rated their comfort with wearing the Adiana matrices as "excellent". The vast majority of women rated their overall satisfaction with the Adiana System as "very satisfied".

The Adiana System does not contain drugs or hormones.

XIII. Panel Recommendations

XIV. CDRH Decision

XV. Approval Specifications

III. DEVICE DESCRIPTION

III. A. OVERVIEW OF ADIANA TRANSCERVICAL STERILIZATION SYSTEM

2.2. Adiana Transcervical Sterilization System

The Adiana Transcervical Sterilization system is shown in Figure 2.1. The system consists of two principal components: The Adiana RF Generator and the Adiana Delivery Catheter containing the Adiana Matrix.

Figure 2.1: The Adiana Transcervical Sterilization System, showing the Adiana RF Generator and the Adiana Delivery Catheter

2.2.1 MECHANISM OF ACTION

The Adiana technique for performing transcervical sterilization involves a two step process:

- First, the epithelial layer in a discrete section of the fallopian tube is destroyed by the controlled application of radio frequency (RF) energy. Removal of the epithelium allows for tissue in-growth, and the wound repair following the RF treatment stimulates this in-growth.

- Following RF treatment, a biomaterial (the "Adiana Matrix") is deployed. The Adiana matrix has been specifically designed to facilitate tissue in-growth. The Matrix is a benign and permanent scaffold which is integrated into the tubal wall. This biological response leads to total occlusion of the tube.

III. B. COMPONENTS

III. B. 1. ADIANA DELIVERY CATHETER AND MATRIX

2.3 Adiana Transcervical Delivery System Components

2.3.1 Adiana Delivery Catheter

The Adiana Delivery Catheter is intended for use with the Adiana RF Generator to perform female sterilization. The Adiana Delivery Catheter contains the Adiana Matrix and includes an electrode sheath configuration at its distal end and a handle at its proximal end. The electrode array consists of 4 stainless steel bands colinearly placed along the distal tip of the catheter. Energy is delivered in a bipolar fashion through the electrode array.

Figure 2.2: The Adiana Delivery Catheter- (FA 011 01); Current handle (Matrix release accomplished by a button press.)

During the course of the EASE clinical trial, a new handle configuration was introduced. Figure 2.4 shows a photograph of the Adiana Delivery catheter with the original handle which was utilized for the initial 335 patients in this study. Following extensive testing and an IDE supplement [redacted] a new handle was introduced on [redacted] which was then utilized for the next 310 patients. Figure 2.2 shows a photograph of the current handle design. The following sections detail the design and operation of the current handle design. Following this section, a comparison between the current design and the original design is provided.

It is important to note that the distal end of the catheter- that part which is in patient contact, as well as the implant- have been unchanged for the entire clinical trial. Figure 2.3 includes a detailed view of the tip of the catheter, which remains the same in both handle designs.

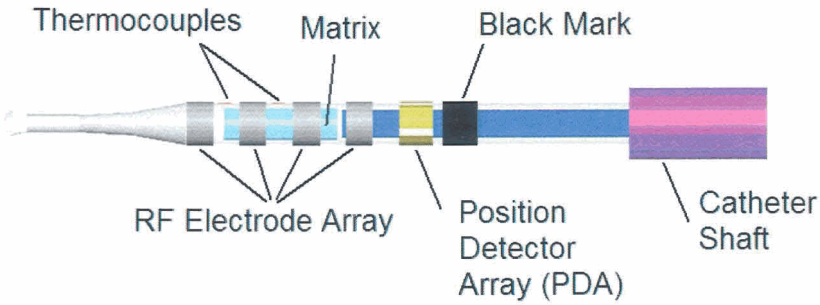

Figure 2.3: Schematic Diagram of tip of Adiana Delivery catheter.

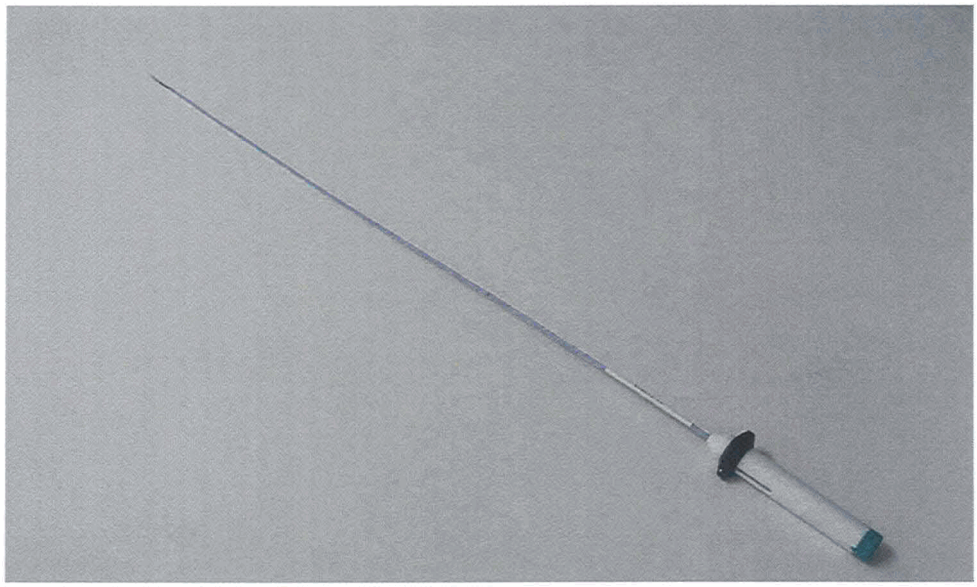

Figure 2.4: The Adiana Delivery Catheter, [redacted]; Original Handle (The Matrix release was accomplished via the black thumb slider.)

The catheter is delivered to the intramural section of the fallopian tube through a conventional hysteroscope via a transvaginal and transcervical approach. Confirmation of device placement within the intramural tube is achieved by means of direct visual assessment through the hysteroscope optics (visually confirming the black mark has reached the tubal ostium) and by the RF Generator via the Position Detection Array (PDA). The Adiana Position Detector Array includes 4 small sensors circumferentially located in four quadrants around the catheter. The sensors detect tissue contact and communicate this information to the RF Generator. When all 4 sensors detect tissue contact, the RF Generator signals that the catheter is in full contact with the tubular fallopian structure. Once the RF Generator has signaled that the catheter is correctly positioned, the

clinician activates the RF generator by pressing the front panel RF button. The clinician may also elect to activate the RF Generator by depressing the foot switch. Following clinician activation via either mechanism, the RF generator then delivers radiofrequency (RF) power in a bipolar fashion through the electrode array, utilizing the thermocouples in the catheter tip to maintain a constant temperature of 64°C for 60 seconds. This creates a superficial lesion within the fallopian tube.

A Matrix release actuator or button is incorporated into the device's handle. After delivery of the RF energy, the clinician deploys the Matrix within the region of the lesion by pressing the button. The catheter is then removed and the procedure repeated with a new catheter on the opposite tube.

2.3.1.1 Physical and Construction Details

[redacted]

2.3.1.2 Device Components

There are four principal components to the Adiana Delivery Catheter. These include:

- Handle and cable (Section 2.3.1.2.1)
- Shaft (Section 2.3.1.2.2)
- Electrode Sheath (Distal Tip) (Section 2.3.1.2.3)
- Matrix (Section 2.3.1.2.4)

[redacted]

[redacted]

[redacted]

2.3.1.2.1 Handle and Cable

Providing an ergonomic hand grip and release actuation control for the clinician, the handle consists of two polycarbonate plastic shells attached together with mechanical fasteners. (Refer to Figure 2.8) Contained within the handle shells are conductor wires, electrical connections, the Matrix release mechanism, and a cable strain relief (refer to Figure 2.9 which shows one of the handle shells removed).

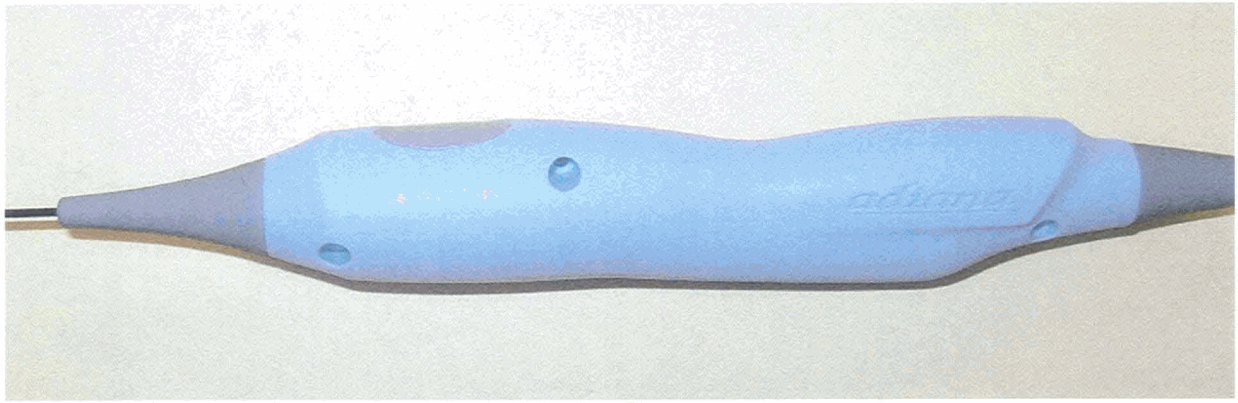

Figure 2.8: Adiana Delivery Catheter Handle

Conductor wires within the catheter sheath/shaft connect the electrode bands and thermocouples on the catheter's electrode sheath with a 'smart block' or connector block that is located in the handle. Conductors from the RF generator cable are also connected to this smart block connector via conductor wires. All connections on the [redacted] (See figure 2.9).

[redacted]

The catheter cable exits the handle via a [redacted] strain relief and is 49cm in length, from the strain relief to the end of the connector. The polysulfone plastic electrical connector contains pins that are soldered to the cable conductors and attached to the cable jacket. In clinical use, the catheter is connected to the RF generator via the RF Generator Cable, which attaches to the Catheter Cable connector on one end, and the RF Generator front panel connector on the other end. (See Fig 2.27).

The Matrix release mechanism consists of a fluid filled dampener and a pre-loaded spring that are assembled into a sliding mechanism. Figure 2.10 shows a photograph of these components, and figure 2.11 shows a perspective drawing of the 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. Section 2.3.1.2 provides a detailed description of the mechanical action of these components.

[redacted]

2.3.1.2.2 Delivery Catheter Shaft

The delivery catheter outer shaft is made from [redacted] tubing with a [redacted] The outside shaft covers the conductor wires, Matrix release mechanism and thermocouple wire and insulates them from other equipment and from the patient. (During operation of the Matrix release, (Section 2.4) the electrode sheath is retracted within the catheter's outer shaft. The outer shaft allows the inner sheath to move freely within while the outside of the shaft is in contact with the hysteroscope.

The proximal end of the shaft is attached within the strain relief by heat fusing a bonding ring onto the shaft, then overmoulding the strain relief onto shaft. The strain relief is mechanically anchored to the handle. (Drawing 3.6).

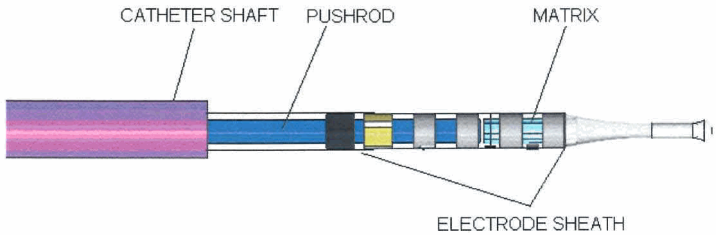

Figure 2.11: Distal tip detail showing relationship between catheter shaft and distal electrode sheath.

2.3.1.2.3 Electrode Sheath (Distal Tip)

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 fabricated from a [redacted] and contains an atruamatic tip, the Matrix, the Position Detection Array (PDA), the electrode sheath assembly, and a black [redacted] band (black mark) located at the distal edge of the PDA. The black mark assists the clinician with visual assessment of placement of the Delivery Catheter into the tubal ostium. A Matrix exit hole is located on one side of the sheath approximately 3 mm proximal to the end of the distal tip. The tapered atraumatic tip is made from [redacted] plastic and is located at the distal end of the electrode sheath.

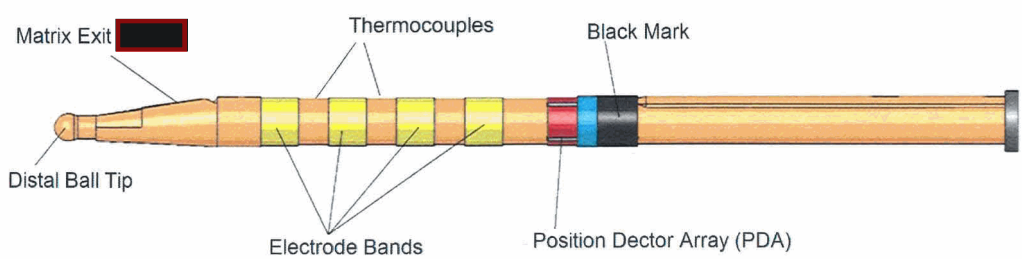

Figure 2.12 – Distal Tip - Electrode Sheath. Surface view of the distal polyurethane sheath with the 4 electrode bands, embedded thermocouples, Position Detector Array and black mark. (The beginning of the outer catheter shaft is seen at the far right.)

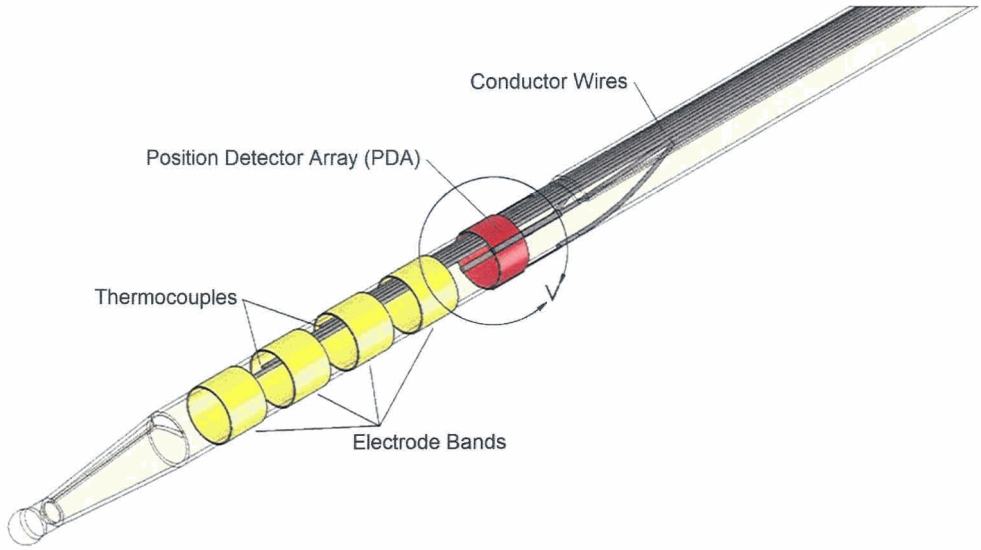

Figure 2.13 – Distal Tip- Electrode Band/Wiring detail. The electrode sheath materials are shown as transparent to highlight the electrical wiring. The PDA, electrode array and thermal sensors are shown.

The electrode sheath assembly is comprised of four band electrodes and two thermocouples. The Delivery Catheter electrodes and thermocouples are arranged on the sheath, one in the middle of the 2nd and 3rd bands, and the other between the 1st and 2nd bands, with the 1st band being the most distal band. [redacted] (See figure 2.13 Band wiring)

Four band electrodes [redacted] are arranged along the distal sheath to create a total electrode array length of 6 mm. The electrodes are [redacted] insulation thermocouples are placed within the

electrode array to allow measurement of tissue temperatures during lesion formation.

The PDA is located on the electrode sheath, approximately 1.0 mm proximal to the most proximal electrode band, (refer to Figures 2.12 and 2.13). The PDA is a circuit made from four independent [redacted] conductor wires and [redacted] plastic tubing. The wires have a short section of insulation removed, which creates a non-insulated tissue contact sensor that is attached circumferentially and equidistant from each other on the tubing, (3, 6, 9 and 12 o'clock).

The circuit senses circumferential tissue contact by the delivery of approximately [redacted] current by the RF generator through the PDA circuitry. When all four sensors on the PDA are in tissue contact, the RF generator observes the electrical impedance created by the current traveling through the tissue. Finally, when a preset threshold is reached, the RF Generator notifies the clinician of proper contact both audibly and visually through a panel display. The RF generator will not allow the clinician to deliver RF power until the PDA circuit signals that all four sensors are in tissue contact.

A full catheter length push rod assembly, made from a [redacted] are located within the electrode sheath and catheter shaft (refer to Figure 3.1 through 3.4). 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.

A lubricious coating [redacted] is applied to the external portion of the sheath material distal to the most proximal electrode band. [redacted]

This material is further described in the Materials Section 4.2.2.6 of this module.

2.3.1.2.4 Implantable Matrix

The Matrix is manufactured from polydimethylsiloxane (silicone). This material is a fully cured solid silicone with a long history of medical device use. The material is acquired from [redacted] The Matrix is a cylindrical shape of approximately 1.60 mm in diameter and 3.5 mm in length, (refer to Figure 2.16). During the manufacturing process a solid core with a diameter of approximately 0.4 mm is created within the center of the matrix.

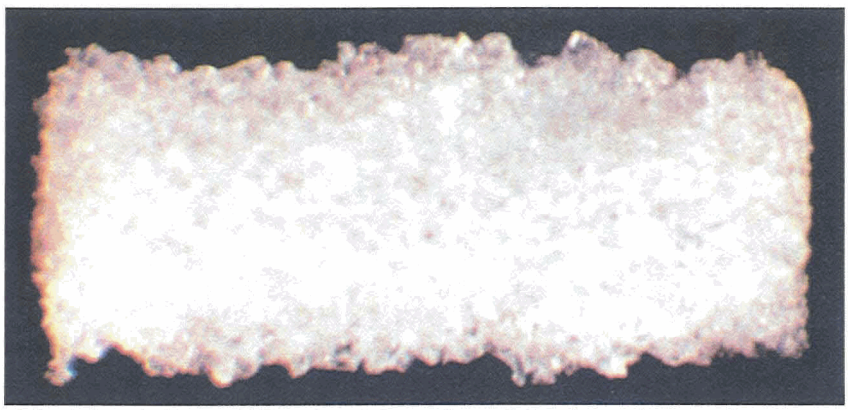

Figure 2.14: The Adiana Matrix. Note that this view shows the outer surface which consists of a semi-random porous architecture.

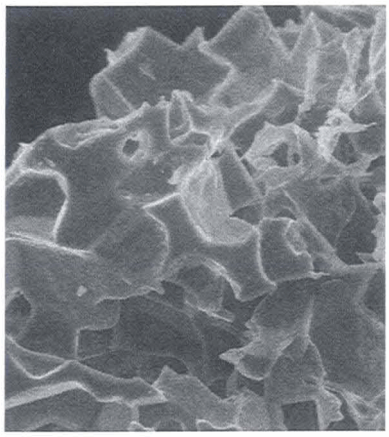

Figure 2.15 The Adiana Matrix; Photomicrograph. This view shows the unique porous internal architecture of the matrix.

Within the Matrix, in the region surrounding the solid core, an internal architecture with a random porous configuration in the range of 40 to 200 microns is created to encourage in-growth of tissue and insure stable long term occlusion (Figures 2.14, 2.15).

To properly position it for delivery, the Matrix is compressed within the electrode sheath. After release from the electrode sheath, the matrix expands to its approximate original shape and volume as permitted by patient anatomy. Figure 1.13 includes an engineering drawing showing the Matrix configuration and internal details. Section 4.1.2.contains data on biocompatibility, and Section 4.2.2.1 includes information on implant material analysis. Matrix performance is discussed in Sections 4.2.3.5.

2.3.1.2 Mechanical Action

The Matrix release mechanism consists of 5 key components:

- fluid dampener/spring
- chassis with
- sliding hub
- latch and
- actuator button

Release of the Matrix is accomplished via the retraction of the electrode sheath while maintaining the Matrix in a fixed location. The push rod assembly forms a rigid, stationary assembly extending from its fixed end, which is attached to the handle chassis, to its distal end, which rests against the proximal end of the matrix. Figure 2.17 shows the proximal hypotube portion of the push rod assembly which is fixed to the chassis and cannot move in relation to it. Also note that the sliding hub is attached to the outer electrode sheath, but is not attached to the underlying push rod. In this figure, the spring is fully compressed, and the sliding hub is fully forward. The latch is holding the sliding hub in this position. The outer sheath, which extends continuously to the distal end of the catheter to form the electrode sheath, is attached to the Sliding Hub. (For clarity, the outer catheter shaft that surrounds the sheath and [redacted] is omitted from the drawing.)

[redacted]