

## SUMMARY OF SAFETY AND EFFECTIVENESS

### I. GENERAL INFORMATION

<b>Device Generic Name :</b>	Implanted Mechanical/Hydraulic Urinary Continence Device
<b>Device Trade Name :</b>	AMS Sphincter 800™ Urinary Prosthesis
<b>Applicant's Name and Address:</b>	American Medical Systems 10700 Bren Road West Minnetonka, MN 55343
<b>PMA Number:</b>	P000053
<b>Date of Notice of Approval to Applicant :</b>	June 14, 2001

### II. INDICATIONS FOR USE

The AMS Sphincter 800™ Urinary Prosthesis is used to treat urinary incontinence due to reduced outlet resistance (Intrinsic Sphincter Deficiency).

### III. DEVICE DESCRIPTION

The AMS Sphincter 800™ Urinary Prosthesis is a small fluid-filled device that is implanted within the body. The device is implanted in men who developed urinary incontinence due to reduced outflow resistance (intrinsic sphincter deficiency, ISD) following prostate surgery. It is designed to restore the natural process of urinary control. The device simulates normal sphincter function by opening and closing the urethra at the control of the patient. The device is made primarily from solid silicone elastomer and consists of three components: a cuff, a pump, and a pressure-regulating balloon (Figure 1). The components are filled with either normal saline or contrast media and are connected to each other with kink-resistant tubing and Suture-Tie or Quick Connect (sutureless) connectors. The device is assembled intraoperatively by the surgeon using 1 of 12 different cuff lengths, a control pump, and 1 of 5 different pressure regulating balloons. The cuff lengths vary from 4.0 cm to 11.0 cm, and the balloon pressures range from 41 cm H<sub>2</sub>O to 90 cm H<sub>2</sub>O (41-50, 51-60, 61-70, 71-80, 81-90 cm H<sub>2</sub>O). The surgeon selects the suitable cuff length by using a cuff sizer with gradations around the urethra.

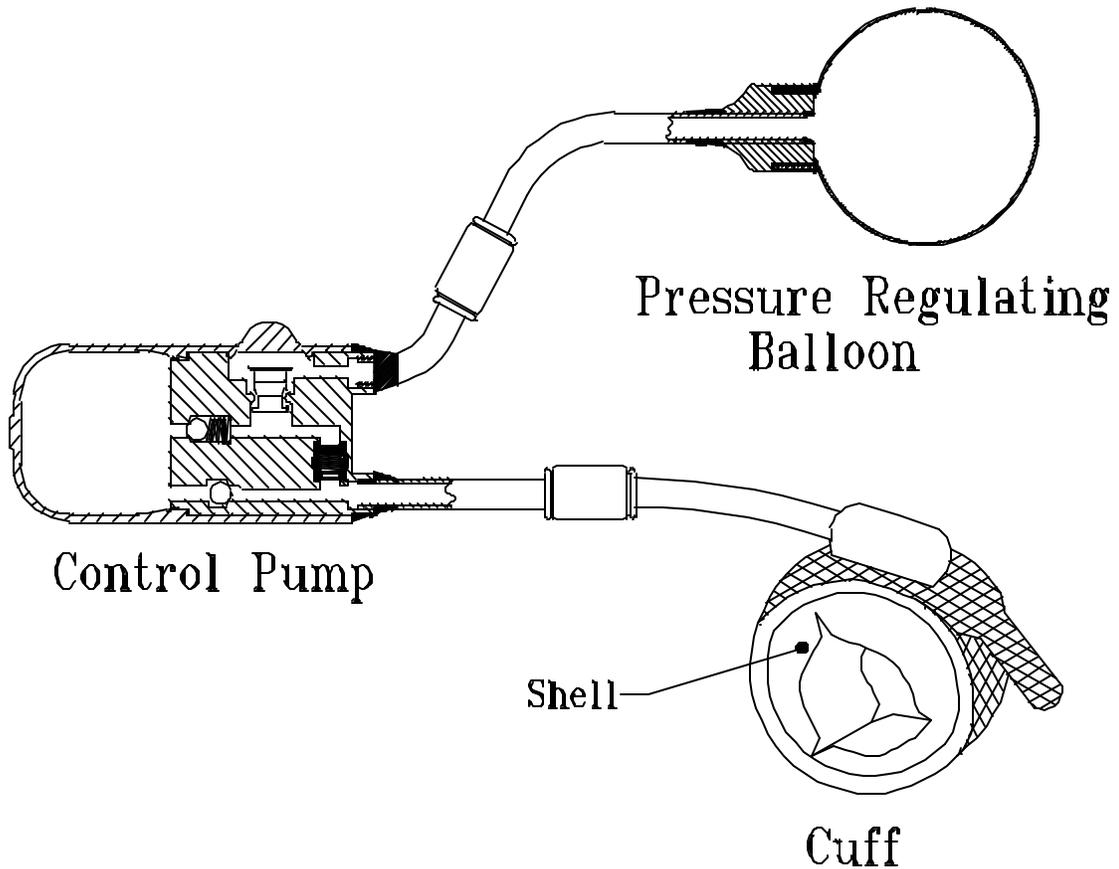


Figure 1. AMS Sphincter 800™ Urinary Prosthesis

### Device Operation

The cuff has an inner shell and outer backing. The inner shell expands when filled with fluid. The cuff is implanted at the bulbous urethra in males. The pump is implanted in the scrotum and the pressure-regulating balloon is implanted in the abdomen. Pressure regulating balloons are designed to maintain cuff pressure within one of 5 narrow pressure ranges, regardless of the volume of fluid emptying or filling that occurs during prosthesis use. The upper part of the pump contains a resistor and valves to transfer fluid to and from the cuff. The lower part of the pump forms a bulb that helps in emptying the bladder. The cuff occludes the bladder neck or urethra by applying gentle pressure around the circumference of the anatomical structure. When the patient wishes to void, he gently squeezes the lower part of the control pump several times. This moves fluid that pressurizes the cuff into the control pump and then on into the pressure-regulating

balloon. As fluid leaves the cuff, it deflates and the urethra opens, enabling the patient to void. The fluid resistor in the pump then automatically allows gradual refilling of the cuff by transferring fluid from the balloon. Within several minutes, the cuff refills and again closes the urethra.

#### IV. CONTRAINDICATIONS

This device is contraindicated in patients whom the physician determines to be poor candidates for surgical procedures and/or anesthesia due to physical or mental conditions.

This device is contraindicated in patients with urinary incontinence due to or complicated by an **irreversibly** obstructed lower urinary tract.

This device is contraindicated in patients with irresolvable detrusor hyperreflexia or bladder instability.

#### V. WARNINGS AND PRECAUTIONS

##### Warnings

1. Patients with urinary tract infections, diabetes, spinal cord injuries, open sores, or skin infections in the region of the surgery have an increased risk of infection associated with the prosthesis. Appropriate measures should be taken to reduce the likelihood of infection. Infection that fails to respond to antibiotic therapy may result in removal of the prosthesis. Infection followed by explanation of the device may result in scarring which may make subsequent reimplantation more difficult.
2. Erosion may be caused by infection pressure on the tissue, improper cuff sizing, improper balloon selection, tissue damage, and component replacement. The cuff may erode around the urethra or bladder neck, or the control pump may erode through the scrotum. The pressure-regulating balloon can erode into the bladder. Acute urinary tract infection can interfere with proper functioning of the device and may lead to erosion of the urethra in the cuff area. Failure to evaluate and promptly treat the erosion may result in substantial worsening of the condition leading to infection and/or loss of tissue.
3. Poor bladder compliance or a small fibrotic bladder may require some measure of intervention including, in some cases, augmentation cystoplasty before implanting the prosthesis.
4. Patients with urge incontinence, overflow incontinence, detrusor hyperreflexia or bladder instability should have these conditions treated and controlled (or resolved) prior to implantation of the device.

5. Do not pass a catheter or any other instrument through the urethra without first deflating the cuff and deactivating the device.
6. This device contains solid silicone elastomers. This device does not contain silicone gel. The risks and benefits of implanting this device in patients with documented sensitivity to silicone should be carefully considered.
7. Surgical, physical, psychological, or mechanical complications, if they occur, they may necessitate revision or removal of the prosthesis. Removal of the device without timely reimplantation of a new device may complicate subsequent reimplantation. The timing of reimplantation should be determined by the treating physician based on the patient's medical condition and history.
8. Product wear, component disconnection or other mechanical problems may lead to surgical intervention. Mechanical complications may include malfunctioning of the components and leakage of fluid. Any mechanical malfunction that does not permit the transfer of fluid from the cuff to the balloon may result in overflow obstruction. Mechanical events should be evaluated carefully by the treating physician, and the patient should consider the benefits and risks of treatment options, including revision surgery.
9. Previous patient history of adverse reaction to radiopaque solution precludes its use as a filling medium for the prosthesis. Instead saline should be used to fill the device.

## **Precautions**

### **Patient Related**

1. Patient selection requires thorough preoperative consultation and evaluation by the physician.
2. Patients should be counseled in order to have a realistic expectation of the physical, psychological, and functional outcome of the implantation of the prosthesis. Although the prosthesis is designed to restore urinary control some patients continue to have a degree of incontinence after this procedure.
3. Patients may experience pain when the device is activated in the postoperative period and during periods of initial use. Cases of chronic pain associated with the device have been reported. Pain with a severity or duration beyond that which is expected may require medical or surgical intervention. Patients should be counseled on expected postoperative course of pain including severity and duration.
4. Tissue fibrosis, previous surgery, or radiation therapy in the area of the implant may preclude implantation of the cuff at the bulbous urethra or bladder neck.

5. Any progressively degenerative disease, e.g. multiple sclerosis, may limit the future usefulness of the implanted prosthesis as a treatment of the patient's urinary incontinence.
6. Adequate manual dexterity, strength, and motivation are required for proper use of the device.
7. Trauma or injury to the pelvic, perineal or abdominal areas, such as impact injuries associated with sports, can result in damage to the implanted device and/or surrounding tissues. This damage may result in the malfunction of the device and may necessitate surgical correction including replacement of the prosthesis. The physician should advise patients of these possibilities and warn them to avoid trauma to these areas.

### **Surgery Related**

1. Improper cuff sizing, improper balloon selection, or other causes may result in tissue erosion, migration of components, or continued incontinence.
2. Component migration can occur if the cuff is sized improperly, if the pump or balloon is not positioned correctly, or if the tubing length is incorrect. Migration can result in pain, complications, device malfunction and surgical revision.
3. Unsuccessful outcomes may result from improper surgical technique, improper sterile technique, anatomical misplacement of components, improper sizing and/or filling of components.
4. Although reinforced tubing has been designed to be more resistant to tubing kinks, tubing kinks may still result from tailoring the connecting tubing to an improper length during the implant procedure.

### **Device Related**

1. If the deactivation valve is closed when the cuff is inflated, fluid cannot transfer from the cuff to the balloon and sustained outflow obstruction may arise as a result:
  - a. In the event of large pressures within the bladder, automatic pressure relief that normally occurs with the device would be prevented. Cycling the device can relieve the outflow obstruction.
  - b. Cycling the device may be difficult if deactivation occurs when the pump bulb is deflated. If unable to cycle the prosthesis, squeezing the sides adjacent to the deactivation button will allow fluid to fill the pump bulb and then the pump can be cycled normally.

- c. Releasing the deactivation valve may require greater pressure than normally used to cycle the device.
2. Pressure changes may occur over time if you fill the balloon with radiopaque solution of incorrect concentration. Follow the instructions in the Operator's Manual to prepare the radiopaque solution with the correct concentration.

## **VI. ALTERNATIVE PRACTICES AND TREATMENTS**

Alternative treatments for stress urinary incontinence due to intrinsic sphincter deficiency include absorbent pads, behavioral techniques, drug therapy, and surgical procedures. Behavioral techniques have proven successful at treating mild cases of stress urinary incontinence (SUI). Drug therapy, including estrogen therapy in women, also produces successful results at treating mild cases of SUI. In more severe forms of SUI amenable to surgical repair, surgical treatments have proven successful. Injectable bulking agents and sling procedures are the two main types of surgery indicated for SUI due to ISD.

## **VII. MARKETING HISTORY**

The applicant submitted this application in response to the final rule published in the Federal Register of September 26, 2000 (Volume 65, No. 187, pages 57726-57732) requiring the submission of a PMA application for Implanted Mechanical/Hydraulic Urinary Continence Device. The AMS Sphincter 800 Urinary Prosthesis was cleared for marketing as a preamendments Class III device through the premarket notification (510(k)) process in 1983. FDA has cleared several premarket notifications for design modifications to the device since its introduction. A CE-mark for the AMS Sphincter 800™ Urinary Prosthesis was received in June 1997. AMS estimates that more than 45,000 AMS Sphincter 800™ Urinary Prosthesis devices have been implanted in patients in over 50 countries worldwide and reports that it has not been withdrawn from any markets for any reason related to safety or lack of effectiveness.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE**

A total of 43 adverse events in 26 patients were reported to be device related in a prospective clinical study. The various device- related adverse events are shown in Table 1 below. Additional details regarding these device-related adverse events and details regarding non-device related adverse events are provided later under "Clinical Studies-Prospective Study".

Table 1. Device Related Adverse Events in Prospective Study

Event Category	Total Events	No. of Patients
Compromised Device function	7	6
Pain/discomfort	6	5
Delayed Wound Healing	5	5
Migration	3	3
Recurrent Incontinence	3	3
Bladder Spasms	2	2
Difficult Activation	2	2
Tissue Erosion	2	2
Infection	2	2
Swelling	2	2
Fistula Formation	1	1
Hematoma	1	1
Hydrocele	1	1
Tissue Erosion/Infection	1	1
Patient Dissatisfaction	1	1
Positional Incontinence	1	1
Wound Infection	1	1
Urinary Retention	1	1
Difficult Deactivation	1	1

## IX. SUMMARY OF PRECLINICAL STUDIES

### A. Materials and Characterization

The materials in the AMS Sphincter 800™ Urinary Prosthesis are predominantly solid silicone elastomers. All the elastomers are platinum-catalyzed, solid silicones. No silicone gel was used in the fabrication of this device. Many of the materials used are the same as the materials used in AMS 700 Series Inflatable Penile Prosthesis Product Line (D970012) (hereafter referred to as AMS 700 Series Penile Prosthes). However, some silicone elastomers not used in the fabrication of the penile prostheses are also used in the construction of the balloon shell, cuff shell and fabric reinforced cuff backing of AMS Sphincter 800™ Urinary Prosthesis. The various safety tests described later under “Biocompatibility Testing” specify which tests were conducted on the new materials and

which were conducted on penile implants and included in this PMA. Furthermore, the safety of these new materials was evaluated by chemical characterization of the saline/ethanol (9:1) and acetone extracts and by *in vitro* and *in vivo* biocompatibility tests conducted on the balloon and cuff components of AMS Sphincter 800™ Urinary Prosthesis. These results show that the materials used in the fabrication of these components were not toxic. The extraction studies and material characterization studies were performed on finished, sterile devices.

**Chemical characterization** of the acetone extracts of the balloon and belt cuff showed that the amounts of small molecular weight components (Molecular Weight <1500, D1-D18) in the extracts were in the same range as the amounts found in AMS Malleable 650 and Dynaflex Penile Prostheses. The amounts extracted by saline/ethanol (9:1) solvent were at least 10-fold smaller than the amounts extracted by acetone.

**Exhaustive extraction** of the AMS Sphincter 800™ Urinary Prosthesis device with methylene chloride and saline/ethanol ((9:1) and characterization of the extracts followed FDA's Draft Guidance for the preparation of PMA application for the Implanted Mechanical/Hydraulic Urinary Continence Device (Artificial Sphincter), May 1, 1995. The results showed that the total amount of silicone extracted in methylene chloride was about 10% of the weight of the device and the low molecular weight silicones (MW <1500) accounted for 25% of the total silicone extracted. Small amounts of Platinum (< 2.2 µg/device), tin (< 17 µg/device) and soluble silica (1.9 mg silicon/device in saline/ethanol extract) were also found in these extracts. The information available in the published literature on these chemicals and the toxicological testing referenced below indicate health risk from these extractable components. As would be expected, the total amount of silicone extracted by a polar solvent such as saline/ethanol was far smaller than the amount extracted by a nonpolar solvent such as methylene chloride.

**Infrared Spectra-ATR-FTIR** (Attenuated Fourier Transform Spectroscopy) analysis showed that the material in the outer surface of each device component having direct tissue contact is polydimethyl siloxane. The surface composition is identical to the bulk composition found in all silicone components. No other materials were detected.

## **B. Biocompatibility Testing**

A battery of *in vitro* and *in vivo* tests were performed to supplement the evidence for safety of the materials obtained from chemical analysis of the device extracts. In these tests cells or whole organisms were exposed to the device extracts or device materials from sterile finished prostheses. The test program followed FDA's *Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials (July 6, 1993)*, and FDA's *Blue Book Memorandum #G95-1, entitled "Use of international Standard ISO-10993, Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing"*. Finished, sterile products were subjected to the complete spectrum of biological tests cited in the Blue Book Memorandum guidance. The majority studies included testing of polar (saline/ethanol) and nonpolar (methylene chloride or

acetone) extracts of the device and/or device components. The following tests were conducted on the AMS Sphincter 800™ Urinary Prosthesis (balloon and belted cuff) or the device extracts:

- Cytotoxicity (L929 mouse fibroblasts)
- Acute Systemic Toxicity
- Intracutaneous Irritation
- Sensitization in Guinea Pig (Magnusson-Kligman Maximization Study)
- Ames Mutagenicity Test
- Mouse Lymphoma Test
- Mouse Micronucleus Test
- Muscle Implantation Test (14-day and 90-day implantation in rabbits)

To provide the worst case scenario of the biocompatibility of silicone elastomers used in the fabrication of the pressure regulating balloon, cuff shell and cuff backing, the above tests were conducted acetone extracts were chosen for testing since acetone is known to extract more silicone than saline/ethanol solvent. No evidence of cytotoxicity, mutagenic effects or significant irritation or toxicity was found in these tests.

Since several silicone elastomers used in the AMS 700 Series Penile Prostheses (D 970012) are also used in AMS Sphincter 800™ Urinary Prosthesis, the following studies performed on penile implant devices were included in the PMA to further document the biocompatibility of AMS Sphincter 800™ Urinary Prosthesis. In these studies substantial amounts of ground silicone elastomer from finished, steam sterilized, penile implant device were implanted subcutaneously in Sprague Dawley male rats. The same 2-year study in the rats provided information on the fate of the implanted material and its effect on host systems (e.g., toxicity, carcinogenicity) as outlined below. The studies included:

- An Acute Pharmacokinetic Study (4-day Study) ,
- Chronic Toxicity Study
- Studies on Reproductive effects, and
- Carcinogenicity Study
- Silicone Migration Study (in Rats)

The acute pharmacokinetic study provided no evidence for transport, excretion or tissue accumulation of implant-derived silicon compounds during the four days following the implantation of the silicone elastomer.

The results from the 2-year rat study showed no evidence of carcinogenic or reproductive effects. Assays of ten distant organs (e.g., kidneys, lungs, liver, brain, spleen, spinal cord, testes, urinary bladder, auxiliary and inguinal lymph nodes) showed that silicon concentrations in these organs from silicone elastomer implanted animals were not significantly different (statistically indistinguishable) from the levels in control animals at

6, 12, or 24 months post-implantation, indicating that silicone or silica did not migrate from the device and accumulate in tissues.

In addition to these studies, a separate immunological study was conducted in male rats. This study was divided into two parts: adjuvant effects study and immunomodulation study. In the adjuvant effects study, the test material (ground silicone elastomer mixed with sodium hyaluronate in phosphate buffered saline) was mixed with a known antigen (bovine serum albumin, BSA) and injected at the same site intramuscularly. In the immunomodulation study, the test material was injected several times over several weeks subcutaneously, followed by a single intramuscular injection of BSA after the last injection of the test material. Its objective was to examine whether silicone elastomer can serve as an adjuvant to potentiate the response to a known antigen and whether it can produce systemic effects on the immune system such that the response to the antigen is altered. These studies showed that silicone elastomer did not produce a measurable enhancement of antibody response (no adjuvant effect) or an alteration of antibody response to BSA (immunomodulation effect).

### **Conclusions from Biocompatibility Studies**

Results from all tests supported the conclusion that the materials used in the AMS Sphincter 800™ Urinary Prosthesis do not produce local or systemic effects and do not constitute a significant health risk to the implanted with the device.

### **C. MECHANICAL TESTING**

A risk analysis, including failure modes and effects analysis (FMEA), was performed to identify the safety and reliability attributes applicable to the AMS Sphincter 800™ Urinary Prosthesis. Appropriate cuff sizes and balloon ranges were tested to evaluate the full range of configurations. Both non-aged and accelerated aged (5 years) samples were tested, using both ethylene oxide sterilized and steam sterilized samples. In all tests, sufficient number of samples were tested to permit meaningful statistical analysis.

#### **Performance Testing**

Performance of the device was evaluated by testing the device and its components for the following performance characteristics:

- Pump squeeze force versus fluid displacement
- Fluid displacement per pump stroke
- Deflation effort, number of pump strokes required for cuff dilation and cuff deactivation time
- Prevention of spontaneous deflation
- Pump output pressure produced by pump squeeze force
- Pump refill time
- Pump deactivation force and activation pressure

- Pump valve leakage, maximum valve back pressure and check valve activation pressure
- Cuff deflation/inflation characteristics
- Balloon deflation/inflation characteristics, maximum volume
- Spontaneous deflation
- Kink resistance tubing performance
- Balloon capacity
- Cuff expansion and maximum pressure

These tests demonstrated that the performance of the device and its components meet the specifications and clinical requirements of the device. The test results also indicated that device performance was not affected by the sterilization method or accelerated aging.

### **Reliability Testing**

Device reliability was evaluated by either subjecting samples to representative *in-vivo* conditions, or to a number of estimated uses likely to exceed the number of uses the actual use of the device. Performance attributes evaluated include:

- Cuff deflation/inflation reliability life cycling
- Control pump deflation/inflation reliability life cycling
- Balloon inflation/deflation reliability life cycling
- Connector/kink resistant tubing connection
- Cuff fold wear resistance reliability life cycling
- Tubing/component adhesive bond reliability

Reliability testing demonstrated that the device and its components exceeded the simulated use conditions equivalent to 10 years.

### **Component Strength Testing**

Device strength testing was conducted in a manner similar to reliability testing. These tests include:

- Maximum cuff pressure, pressure to unbuckle
- Cuff leakage or unbuckling under pressure
- Connector/kink resistant tubing strength
- Kink resistant tubing burst/leak pressure
- Connector/kink resistant tubing leak pressure
- Subassembly adhesive bond strength
- Prosthesis material strength

Component strength testing demonstrated acceptable prosthesis or component performance over the estimated use conditions

## **D. Shelf Life Testing**

A shelf life of 5 years is claimed for the AMS Sphincter 800™ Urinary Prosthesis. This shelf life is based on both accelerated aging studies for sterility, packaging and performance (functionality) as well as real time studies for packaging integrity and performance. Since the packaging system is the same for the currently marketed AMS 700 Series Penile Prostheses (D970012), Acticon Neosphincter (H990003) and AMS Sphincter 800™ Urinary Prosthesis, and since this system is known to maintain the device sterility and functionality from the history of marketing thousands of devices for 10 years, validation of accelerated aging studies on sterility with real time studies are not considered necessary. The accelerated aging showed that the packaging configuration would provide physical protection and sterile barrier for a 5-year shelf life with a 2-year margin.

## **X. CLINICAL STUDIES**

Three clinical studies, all conducted by American Medical Systems, are described in the PMA to document the safety and effectiveness of the AMS Sphincter 800™ Urinary Prosthesis. These are referred to as the Prospective Study, the PIF (Patient Information Form) study, and the Retrospective Study. The Prospective Study is the smallest and the PIF Study, the largest study. All the 3 clinical studies were conducted on male patients. In addition, the PMA contains summaries of data presented in numerous published articles.

### **Prospective Study**

The main objective of the Prospective Study was to validate the 5-year revision free rate of 75% (within 10% variability) estimated in the PIF Study. borrowing data from the PIF Study and using Bayesian statistics. Since the device is a preamendment device and is not subject to IDE regulations, the Prospective Study was a non-IDE study. In addition, since the Prospective Study had only 2-year follow up, the 5-year revision free rate of 75% was calculated by borrowing 90% of the data from the PIF study and using Bayesian statistics.

### **Study Design**

The Prospective Study was conducted as a multi-center, non-randomized clinical study to demonstrate that the AMS Sphincter 800™ Urinary Prosthesis can be surgically implanted without serious adverse sequelae to provide an acceptable level of continence and thereby, improve the quality of life of the patients implanted with AMS Sphincter 800™ Urinary Prosthesis. The pre-implant experience of the patients served as the control for the evaluation of effectiveness. Safety data related to adverse events, surgical revisions, diagnoses and health status evaluations were captured on case report forms. Patient self-administered evaluations related to quality of life, health status, and continence status (references provided later in the Endpoints Section). In addition, patient

and physician assessments of continence were measured on a recognized, standardized instrument. The cut off date for the data submitted in the PMA was October 4, 2000.

### **Patient Selection**

Only male patients were eligible for enrollment in the study. The following selection criteria were used for enrollment.

#### **Inclusion Criteria:**

1. Patient has decided to be implanted with an AMS Sphincter 800™ Urinary Prosthesis for the treatment of urinary incontinence.
2. Patient had confirmed urinary incontinence for a minimum of 6 months with the primary etiology being Post-Transurethral Resection (TUR), Transurethral Resection of the Prostate (TURP), or Radical Prostatectomy.
3. Patient was willing and able to give informed consent.
4. Patient was willing to return for follow-up evaluations and questionnaire completion.
5. Patient was given information pertaining to alternative therapies available for the treatment or management of urinary incontinence and was informed of all possible risks related to implantation of a urinary prosthesis.
6. Any pre-existing urological conditions had been treated and resolved or were under control.
7. Patient must be a good surgical candidate,
8. Patient must be 21 years of age or older.

#### **Patient Exclusion Criteria**

Any one of the following criteria excluded the patient from the study.

1. Patient had previously received an artificial urinary sphincter prosthesis implant or other urogenital implant.
2. Patient had a history of sensitivity to silicone.
3. Patient did not speak English (the exclusion of non-English speaking patients was necessary because the quality of life survey instruments had not been validated in non-English speaking populations).

4. Patient's reading level was judged to be inadequate for reading and understanding the patient labeling (reading must have been at least seventh grade level).
5. Patient's health would have precluded completion of the follow-up, including terminal illnesses.
6. Patient refused to, or was unable to, comply with the requirements of the protocol.
7. Patient's urinary incontinence was less than 6 months in duration, post- TUR, TURP, or radical prostatectomy and/or primary etiology of incontinence was not one of the above three procedures.
8. Patient presented with a neurogenic bladder condition that was not treatable or controllable by pharmacological or alternative methods.
9. Patient had a history of connective tissue or autoimmune conditions.
10. Patient had uncontrolled diabetes as confirmed by glycosylated hemoglobin measurement.
11. Patient had post void residual urine  $\geq 75$  cc.
12. Patient had an active abscess or infection.

### **Demographics/Etiology**

Eighty-seven (87) male patients who developed urinary incontinence following prostate surgery were enrolled in the study. Except for 1 Black and 1 Asian, all other patients (85, i.e., 97.7%) were Caucasian. Of these 87 patients, 76 (87.4%) were post- prostatectomy patients and 11 (12.4%) were post- TUR (transurethral resection) patients. Mean age of the patients was 67.7 years.

### **Medical History**

Fifty-eight patients had cardiovascular conditions, 40 had musculoskeletal conditions, 8 had neurological conditions, 15 had bladder dysfunction (e.g., fibrotic bladder, detrusor instability, low bladder capacity), 3 had chronic urinary tract infection (UTI), 46 had erectile dysfunction and 37 had strictures. All the patients were required to complete a Connective Tissue Disease Screening Questionnaire (CTD-SQ) prior to implantation. Eighty-five (85) of the 87 patients enrolled in the study completed the CTD-SQ. None of the patients showed positive results on rheumatology review of the responses to the questionnaire.

### **Pre-Implant Urological Procedures**

Of the 87 patients enrolled, 15 had pelvic radiation, 9 had pelvic surgery, 8 had bladder neck surgery, 7 had TUR-Prostate (not primary surgery), 33 had none and 32 had other procedures. Some of the “other procedures” were bladder neck contracture, bladder neck incision, radiotherapy for prostate cancer, dilatation, Direct Vision internal Urethrotomy, suprapubic prostatectomy and suburethral sling.

### **Pre-Implant Management of Incontinence**

The surgical implantation of AMS Sphincter 800™ Urinary Prosthesis was not the first treatment or management option for the 87 enrolled patients. Eighty-one patients reported using one or more methods. The most commonly used management method was absorbent pads (80 patients). Twenty-six patients used pharmacologic treatment, 31 patients had periurethral collagen injections, 21 used Cunningham clamp, 15 used condom catheter, 9 had biofeedback therapy, 4 had electrical stimulation, 13 had other behavioral modification techniques and 3 had urological surgery.

### **Deactivation of AMS Sphincter 800™ Urinary Prosthesis**

After surgical implantation of AMS Sphincter 800™ Urinary Prosthesis in the patient, the surgeon deactivates the device by pressing the deactivation button in the pump to empty the fluid in the cuff and allow healing of the urethral tissue for 4-6 weeks. In the deactivated state, the cuff remains empty and the patient manages his incontinence with other methods such as absorbent pads. At the follow-up visit after the healing period, the physician activates the device. The activation is achieved by squeezing the lower part of the pump implanted in the scrotum. On activation, the cuff is refilled with the fluid to close the urethra and maintain continence.

### **Follow-up**

The first office visit was scheduled 4-6 weeks post-implantation for activation of the device and incontinence assessment. If the assessment did not occur at this Activation visit, a First Post-Activation follow-up visit was scheduled before the 6-month visit. Patients were followed at 6, 12, 18 and 24 months post-implant. Sixty-seven patients had 6-month follow-up, 60 patients had 12-month follow-up, 55 had 18-month follow-up and 41 patients had 24-month follow-up.

### **Patient Accountability**

Of the 87 patients enrolled, one patient withdrew before implantation and one patient was not implanted as of the data cut-off date. Of the remaining 85 patients implanted, one patient had the device removed prior to activation due to infection and activation data

was not submitted for 4 patients prior to database closure, leaving 80 patients with activation data.

Thirteen (13) of the 87 enrolled patients did not complete the study. Three of the withdrawals were due to deaths and they were determined by the investigators not to be related to the device. The reasons for discontinuation are shown in Table 2 below.

Table 2. Reasons for Patient Discontinuation from the Prospective Study

	n=87	%
Reason		
Change in Medical Condition*	3	3.4
Patient Death	3	3.4
Device Explanted**	4	4.6
Missed Visits	2	2.3
Withdrew Prior to Implant	1	1.1

8 patients were withdrawn by investigators and 5 patients withdrew themselves.

\*Withdrawal due to prostate cancer (2) and progressive dementia (1).

\*\* Device Explanted, not reimplanted, Erosion (1); Erosion due to Foley Catheter placement for unrelated procedure (1); Infection and Pain related to urethrocutaneous fistula (1); In fection following Y-V plasty for bladder neck contracture unrelated to device (1).

## Endpoints

The primary effectiveness end point was to evaluate the effect of AMS Sphincter 800™ Urinary Prosthesis on quality of life using an Incontinence Impact Questionnaire (IIQ)(Schumaker et al, Quality of Life Research, 3:291-306, 1994)). The IIQ is a validated instrument designed to assess the impact of incontinence on several subscales, including physical, social and emotional scales. The secondary effectiveness endpoints used Health Status Questionnaire (HSQ)(Health Outcomes Institute, HSQ 2.0, 1993 and RAND 36-item Health Survey, 1.0, 1986), and Rosenberg Self-esteem Scale (Rosenberg M. Society and the Adolescent Self Image, Princeton University Press, 1965) for measuring the effect of the device on general quality of life. The HSQ is a slightly modified version of the MOS-20 that was validated as part of Rand Corporation's Medical Outcomes study. The HSQ added 3 questions to MOS-20 about patients's feeling depressed during 2 years after the device implantation. In addition, the physician and patient also evaluated the improvement in patient's incontinence after the sphincter implantation. The primary safety objective or endpoint of the study was to verify by Bayesian analysis that the AMS Sphincter 800™ Urinary Prosthesis has 75% (within delta of 10%) revision free rate found in the PIF Study.

## Effectiveness

### Primary Effectiveness Endpoint: Incontinence Impact Questionnaire

The Incontinence Impact Questionnaire used for determining primary effectiveness is a 30-item, validated, self-administered questionnaire designed to assess the impact of urinary incontinence on several aspects of patient's life, including physical, emotional, social and sexual. Incontinence Impact was measured pre- and post- implant at 6, 12, 18 and 24 months. Thirty-nine (39) patients answered the IIQ at 24 months post-implantation. The higher score indicates greater impact of urinary incontinence on the quality of life. At 2-year follow-up, the mean score was 51, compared to pre-implant score of 143. The mean pre-implant score was significantly higher ( $p > 0.001$ ) than the mean score at all follow-up visits, indicating statistically significant improvement in the patient's quality of life.

### Secondary Effectiveness Endpoints

Patient responses to Health Status Questionnaire and Rosenberg Self-esteem Questionnaire were also evaluated at all four follow-up visits. Thirty-eight (38) patients responded to these questionnaires at 24 months post-implantation. The HSQ was used to assess non-illness aspects such as physical functioning, social functioning, energy/fatigue, pain, health perception and emotional problems. No significant improvement was noted in the health status of the patients at 24-month follow-up. The responses to Rosenberg Self-esteem Questionnaire were used to assess changes in patient self-esteem. In this self-esteem evaluation, the scores ranged from 0 to 6, with a score of 6 indicating high self-esteem. At 2-year follow-up, the mean self-esteem score was 4.1 compared to the mean pre-implant score of 3.5, indicating an increase in self-esteem after the AMS Sphincter 800™ Urinary Prosthesis implantation. The increase in self-esteem scores was statistically significant. The positive impact of the device on patients' lives observed in this clinical study is consistent with the results reported in the literature (Haab *et al*, Journal of Urology, 158:435-439 (1997); Litwiller *et al*, Journal of Urology, 156:1975-80 (1996); Fleshner and Herschorn, Journal of Urology, 155: 1260 (1996)).

Physician and patient assessments of incontinence status after AMS Sphincter 800™ Urinary Prosthesis implantation are shown in the Table 3 below.

Table 3. Patients' Incontinence Status after AMS Sphincter 800™ Urinary Prosthesis Implantation.

Evaluator	Follow-up	# Patients	Dry	Up to 3 pads/day
Physician	1-year	43	63.6%	34.1%
Physician	2-year	30	73.3%	23.3%
Patient	1-year	60	61.7%	36.7%
Patient	2-year	41	65.9%	31.7%

--	--	--	--	--

These results show that there was no significant difference between physician’s and the patients’ assessment of the improvement in patient’s incontinence.

**Sexual Function**

A question in regard to sexual function was also included in the IIQ. The question asked patients how the device affected their sexual relationship: not at all, slightly, moderately or severely. Forty-six of the 87 enrolled patients reported erectile dysfunction pre-implant, leaving 41 patients with erectile function. According to the information provided in the PMA, although only 16 of these 41 patients had 2-year follow-up, none of the patients reported erectile dysfunction attributable to the device at any of the follow-ups and there was also no report of sexual dysfunction in the sponsor’s database or in any of the numerous publications on the device. In their publication, Litwiller et al reported improvement in sexual function in 7 of the 50 patients that they followed.

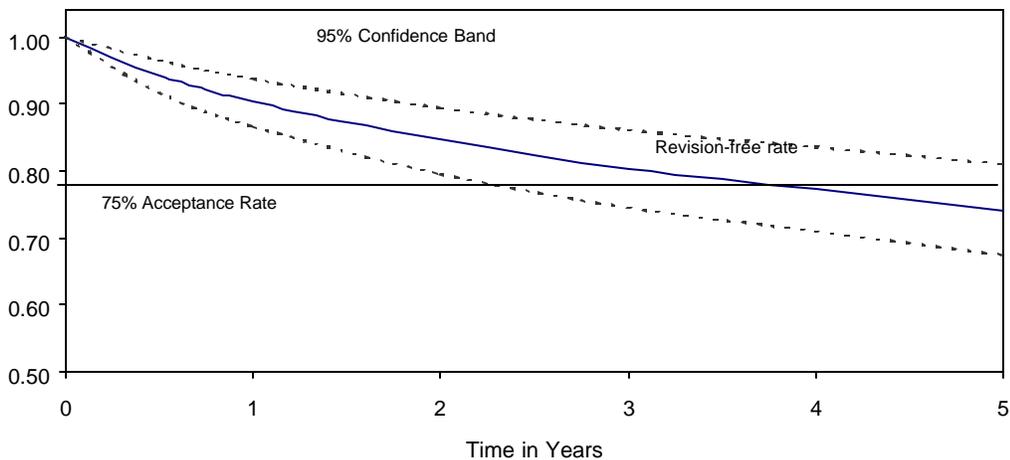
**Safety**

**Primary Safety Endpoint: 5-year Revision-Free Rate**

The primary safety endpoint of the study was to demonstrate that the 5-year revision-free rate (i.e., the device or its component does not need replacement or removal) was not less than 65% (75% minus delta of 10%). Since the Prospective Study followed patients for only 2 years, only the 2-year revision-free rate could be obtained directly. The 2-year revision-free rate was 68.35% and the 1-year revision-free rate was 90.5%. An estimated 5-year revision-free rate of 74% with 95% confidence interval is shown in Figure 2. The 5-year revision-rate was calculated borrowing a large amount of data collected on 875 patients) in the PIF Study and using Bayesian statistical methods.

**FIGURE 2**

**Estimated 5-year revision-free rate of AMS Sphincter 800**



Of the 85 implanted patients, 14 patients (16.5%) required a total of 15 revision surgeries over a period of 2 years. Two revisions in 2 patients were not considered device-related. One of these two patients had an infected wound and the other patient had pain at the base of the penis pre-implant and in the scrotum post-implant. Four of these 14 patients underwent device removal and subsequently exited from the study. The remaining 10 patients underwent device replacement or revision and remained in the study. Details about the revisions in the Prospective Study are presented with revisions in PIF and Prospective studies (Table 4).

### Device Related Adverse Events

As pointed out earlier, a total of 43 adverse events in 26 patients were reported to be device related. The various device- related adverse events are shown in Table 4 below.

Table 4. Device Related Adverse Events in Prospective Study

Event Category	Total Events	No. of Patients
Compromised Device function	7	6
Pain/discomfort	6	5
Delayed Wound Healing	5	5
Migration	3	3
Recurrent Incontinence	3	3
Bladder Spasms	2	2
Difficult Activation	2	2
Tissue Erosion	2	2
Infection	2	2
Swelling	2	2
Fistula Formation	1	1
Hematoma	1	1
Hydrocele	1	1
Tissue Erosion/Infection	1	1
Patient Dissatisfaction	1	1
Positional Incontinence	1	1
Wound Infection	1	1
Urinary Retention	1	1
Difficult Deactivation	1	1

The number of patients exceed 26 since the same patient had more than one type of adverse event. Only one unanticipated adverse event was reported involving Reactive Hydrocele with pain, discomfort and swelling. Thirteen of the 43 events reported above were resolved with no intervention. The remaining events required medical and/or surgical intervention, including revision surgeries.

### **Non-Device Related Adverse Events**

A total of 129 events in 85 patients were reported that were not related to the device. Sixty-three (63) events were categorized as urogenital in nature. Twenty cardiovascular events occurred in 18 patients and 14 musculoskeletal events occurred in 11 patients. None of the musculoskeletal events were considered related to the sphincter device by the physician. AMS supported the physician's determination by noting that the published literature on silicone devices does not show any causal relationship between silicone and any suspected autoimmune diseases.

### **PIF Study**

As indicated earlier, the PIF Study is the largest (12713 male patients) and is based on the information contained in the patient information forms returned to AMS by implanting physicians after implantation of AMS Sphincter 800™ Urinary Prosthesis and/or replacement of the device or its component. The forms typically provide information on the medical history of the patient, etiology of incontinence, date of original implantation surgery, cuff location, replaced component, date of revision surgery and reason for revision. The forms do not contain information about the effectiveness of the device and they do not provide information on adverse events associated with the device other than the adverse event or reason for the revision surgery. Therefore, the data collected under the PIF Study is essentially limited to information regarding revisions and survival of the device.

### **Demographics and Etiology**

The PIF Study patients were implanted with AMS Sphincter 800™ Urinary Prosthesis during 1995-1999. The PIF database referenced in the PMA has a total of 12713 males, 96 females and 262 children. Only the data collected on males were used for the estimation of a revision-free rate and evaluation of the reasons for revision for comparison with the results of the Prospective Study. Although the PIF Study did not have the same eligibility criteria as the Prospective Study, they were close in regard to several criteria. For instance, average age of the PIF patients was 68.5 years versus 67.7 years of the Prospective Study. The etiology of the PIF Study male patients with 77.4% post-prostatectomy and 6.65% post-TUR closely matched the etiologies of the Prospective Study population. In regard to prior treatments, only 8.1% PIF patients had urethral bulking injections compared to 36.8% in the Prospective Study. Eighty five percent (85%) of PIF males had the cuff placed at bulbous urethra, compared to 100% in the Prospective Study. These characteristics show a close similarity of patients in both

studies for comparison of revision-free rates and to qualify the use of data from the PIF Study to estimate the 5-year revision-free rate for the Prospective Study patients, using Bayesian statistical methods.

### **Revision Rates and Reasons for Revision**

The data presented in the PMA shows that the overall 5-year revision-free (device survival) rate for the AMS Sphincter 800™ Urinary Prosthesis was 75%. A comparison of the reasons reported for revision surgeries in other studies is presented in table 4

### **Retrospective Study**

The Retrospective Study is intended to provide both safety and effectiveness information over long-term follow up as long as 9 years. In this study, 390 male patients were implanted with the AMS Sphincter 800™ Urinary Prosthesis to treat urinary incontinence following prostate or sphincter surgery. Radical prostatectomy was the most common etiology (65.6%) and TUR-prostate was the next common etiology (28.5%). The device was implanted in the patients between 1987-1990 at 12 centers in the U.S. Post-implant data was obtained for 356 patients.

The limitation of this study is follow-up times were not specified and physician follow-up occurred on only 19.5% (76/390) of the implanted patients. It is unclear how many patients were followed at each follow up interval. There is also no data on when revision surgeries were done. Therefore, it was not possible to calculate a revision-free rate using Kaplan-Meier method to compare with rates estimated in the PIF Study and Prospective study. Disregarding device revisions, the probability of device use for 9 years in 323 patients was estimated to be 83.9%.

### **Revision Rates and other Information**

This study collected general information on the number of revisions, reasons for revision, and patient satisfaction with the device. The revision rates in this study are presented in Table 4 along with similar information for the Prospective and PIF Studies.

### **Effectiveness: Degree of Continence**

The Retrospective Study reports Physician and Patient Assessments on the degree of continence achieved without specifying when the assessment was made. If the time of assessment is not considered, continence rates are reported as follows. Physician follow-up on 79 patients notes 8 (10.1%) were dry, 17 (21.5%) required no protection and 40 (50.6%) required up to 3 pads/day. Telephone interview on 142 patients reports 48 (33.8%) were dry, 62 (43.7%) required no additional protection and 12 (8.5%) required up to 3 pads a day. If the criterion of up to 3 pads/day is accepted as a reasonable degree of continence, this study data of 82-84% are in good agreement with the Prospective

Study results. However, it is important to note that physician follow-up noted only 10% of the followed patients as completely dry.

### Comparison of Revision Rates for Prospective, PIF and Retrospective Studies

Table 5 below provides stratified data by each reported reason for revision in Prospective, PIF and Retrospective Studies. Under the PIF Study and Retrospective Study, more than one reason may have been cited for a single revision. Therefore, in order to stratify this revision data by reason, all occurrences were included and presented as “%reason”. The total number of reasons therefore exceeds the total number of revisions reported for these two studies.

Table 5: Reasons for Revision in 3 Different Studies

Revision Reason <sup>a</sup>	Prospective Study (n=85)		PIF Study (n=12713)		Retrospective Study (n=356)	
	% revisions (# revisions)		% reason (# reasons) <sup>b</sup>		% reason (# reasons)	
Infection	2.4%	(2)	2.3%	(297)	8.1%	(29)
Infection/erosion	1.2%	(1)	-----		-----	
Erosion	2.4%	(2)	3.6%	(451)	22.5%	(80)
Recurring Incontinence	2.4%	(2)	5.7%	(724)	42.4%	(151)
Fluid Loss	-----		2.3%	(298)	9.3%	(33)
Fluid Transfer impaired	-----		0.3%	(38)	-----	
Pressure too low	-----		1.1%	(140)	-----	
Mechanical Malfunction	3.5%	(3)	0.7%	(89)	13.8%	(49)
Migration/Malposition	3.5%	(3)	0.4%	(46)	4.8%	(17)
Iatrogenic Complications	-----		0.4%	(51)	0.6%	(2)
Reimplantation/ Replacement	-----		-----		3.1%	(11)
Pain	1.2%	(1)	0.2%	(22)	1.4%	(5)
Patient Dissatisfaction	1.2%	(1)	0.2%	(27)	1.7%	(6)
Other <sup>c</sup>	----		2.4%	(305)	----	
Not indicated	----		1.9%	(242)	----	

<sup>a</sup> Note that some adverse events in the table such as fluid loss, pressure too low, fluid transfer impaired and malposition could fall into the category of mechanical malfunction or iatrogenic error. Since information is not available to place them in either category, they are listed separately.

<sup>b</sup> Numbers of reasons can vary for the same percentage due to rounding.

<sup>c</sup> Other includes: double cuff, pressure too high, unable to activate, unable to deactivate, atrophy, difficult to operate, urinary retention, air in the system, hematoma.

Table 6 presents the percentage of patients revised during a specified follow up period, the average number of revisions performed on patients requiring a revision and the total number of revisions performed per 100 patients in the Prospective, PIF and Retrospective Studies. This table shows that the percentage of patients who underwent revision surgery and the number of revisions per 100 patients are almost the same in both Prospective and PIF studies, but much higher in the Retrospective Study. Longer follow up (9 years) may be the reason for higher revision rates in the Retrospective Study.

Table 6. Revision Rates in 3 Different Studies

Type of Study	Prospective Study, 85 Patients. over 2 years	PIF Study, 12713 Patients over 5 years	Retrospective Study 356 Patients over 9 years
% Pts Revised	16.5% (14/85)	15.8% (2014/12713)	46.1% (164/356)
Average # of Revisions per Pts. Revised	1.07 (15/14)	1.05 (2116/2014)	1.93 (317/164)
# of Revisions per 100 Pts.	18 (15/85)	17 (2116/12713)	89 (317/356)

### **Published Reports of Clinical Experience**

Published reports of clinical experience using AMS artificial urinary sphincters dates back to 1973 when Drs. Scott and Bradley reported five successful cases using AMS' first fully implantable hydraulic urinary prosthesis. For the period 1985-2000, 67 articles appeared containing clinical experience on 4,127 AMS artificial urinary sphincter recipients. Analysis was not performed on this group of patients. The literature for this period includes long-term results for multiple patient series equal to or greater than 100 patients. A review of the articles showed successful outcomes (acceptable continence) ranging from 74%-100% and complications were either manageable through medical intervention or resolved without intervention. Erosion and infection were manageable and within acceptable rates for prosthetic surgery. Design modifications have improved mechanical reliability. Several studies measure patient satisfaction using standardized instruments. The results generally found high rates of satisfaction among AMS 800 patients. Patient satisfaction did not depend on achieving total continence and was not affected by revisions.

A selection of published reports on AMS Sphincter 800™ Urinary Prosthesis is summarized below. Most of these reports or studies are selected on the basis that they discuss the outcome in a group of men greater than 100. However, a few reports on less than 100 men are also selected to illustrate a specific effect of the device such as the effect on quality of life or the effect of a design change (e.g., double cuff).

Hajivassiliou (European Urology, 35, 36-44(1999)) performed a meta-analysis using several reports published during 1985-1993 on 2,606 patients implanted with an AMS Sphincter 800™ Urinary Prosthesis to treat urinary incontinence due to ISD of various etiologies. Only 60% of these patients were post-prostatectomy patients in comparison with 87% in the Prospective Study and 77% in the PIF Study. The calculated global success rates and complication rates are shown in the Table 6 presented below.

TABLE 7 Calculated global success rates and complications of the AMS 800. Meta-analysis from 2,606 patients

Category	Global rate (%)
Improved continence	88.1
Fully continent	73.0
Revisions (total)	31.9
Urethral erosion	11.7
Infection	4.5
Mechanical complications	13.8

*Data from Hajivassiliou 1999*

The table shows that 73% of the implanted patients became continent and a total of 32% implanted patients required at least one revision. Fifty percent of the revisions were performed within 8 months and 90% within 3 years of implantation. Mechanical failure accounted for 14% of the complications.

Hajivassiliou also conducted a retrospective review of patient reports on complications following the implantation of AMS Sphincter 800™ Urinary Prosthesis during a period between February 1986 and June 1994 (8.4 years) in FDA database and found 4130 complications in 3508 patients. Since the device has been reported to be implanted in an estimated 20,000 patients all over the world by AMS, the global complications rate was estimated to be 21%. Mechanical malfunctions and complications accounted for 22.1% of the total complications. Failure of the pump accounted for 35.6%, cuff related complications accounted for 43.8% and balloon related complications accounted for 12.6% of the total mechanical complications. In addition, 12.9% of the reported complications in the database were due to infections. Any comparison of these rates with the rates of complications observed in the Prospective Study, PIF Study or Retrospective Study should note that only 60% of the patients in Hajivassiliou's analysis were men with prostatectomy etiology and the rest were children and women.

Even though the global rates were adjusted to account for different numbers of patients in each study, the author notes that many of the small cohorts may have a significant bias depending on whether follow-up documentation was done under "good clinical practice" conditions.

Incontinence improved in nearly nine out of ten patients. About seven out of ten patients were dry. The global rate of mechanical malfunctions was 13.8%. Cuff leaks due to fold wear were the most frequent cause of mechanical failure. A surface treated cuff was introduced in 1983 and the incidence of leakage decreased from 12.5% to 1.3%. Over one in ten patients experienced urethral erosion while the infection rate was less than 5%.

The calculated global urethral erosion rate was 11.7%. The balloon pressure in the cases with urethral erosion was not reported consistently in the literature. In one study (Furlow 1981), all patients with urethral erosion had been implanted with balloons  $>80$  cm H<sub>2</sub>O. None of the patients with balloons  $<70$  cm H<sub>2</sub>O had urethral or bladder neck erosion. Self-catheterization has been reported as an adjunct to AMS Sphincter 800™ Urinary prosthesis implantation. The low rate of post-catheterization erosion reports (5) in this review indicates that careful self-catheterization may be safe. Hajivassiliou concludes that the AMS Sphincter 800™ Urinary Prosthesis implanted in carefully selected patients has a high success rate and a low complication rate. Patients with adverse implantation features (e.g. pelvic irradiation) should not be deprived of the treatment option if meticulous technique (including primary deactivation) is adhered to and patient selection is appropriate.

Elliott and Barrett (*Journal of Urology*, 159, 1206-1208 (1998)) reported on 323 patients who received AMS Sphincter 800™ Urinary Prosthesis from one surgeon between 1983 and 1994 for correction of severe urinary incontinence. The patients were followed for at least 18 months. The mean follow up was 68.8 months. Of the 323 patients, 313 were men and 10 were women. In their publication, they separated mechanical and nonmechanical failures. They also analyzed reoperation rates before (during 1983-87) and after (1988 to 1994) the introduction of the narrowback cuff. Their results show that the use of narrow back cuff significantly decreased reoperation rates and failure rates as follows: 42% (58 of 138) patients in the pre-narrow back cuff group required one revision surgery compared to 17% (31 of 184) patients in the narrow back cuff group. Using Kaplan-Meier statistical analysis, the 5-year product survival (revision-free rate) was calculated to be 75% for the narrow back cuff device. Mechanical failure occurred in 21% (29 cases) with the pre-narrow back cuff and 8% (14 patients) with the narrow back cuff. Mechanical failures consisted of cuff leak, pump malfunction, balloon leak, tubing leak, tube kinking, pump leak and connector separation. Nonmechanical failures developed in 17% (24 cases) with the pre-narrow back cuff versus 9% (17 cases) with the narrow back cuff. Nonmechanical failures involved cuff erosion, infection, decrease in cuff size or increase in balloon reservoir pressure, pump malposition, tubing erosion and tandem cuff placement. Ultimately 437 operations were required in 323 patients, of whom 234 (72%) required no further surgical intervention at a mean follow up of 68.8 months.

Leo and Barrett (*Journal of Urology*, 150, 1412-1414, (1993)) also report on the success of narrowback cuff design. They analyzed the results on 144 patients (136 male and 8 female). Mean follow up was 28 months. The cuff was placed around the bulbous urethra in 107 patients and around the bladder neck in 37 patients (29 male and 8 female). One hundred and five (105) patients had radical or subtotal prostatectomy. They state that “two of the most clinically significant complications are recurrent incontinence caused by underlying urethral tissue atrophy and erosion of the cuff through the smooth muscle of the urethra”. The narrow back cuff design was introduced in 1987 to address these complications. Of the 144 patients, 125 (87%) required no revision, and therefore, the reoperation rate was 13%. The authors conclude that this design change and the use of the

4.5 cm cuff with the 61-70 cm. pressure balloon decreased the incidence of cuff erosion and the need for reoperation for inadequate cuff pressure. On the basis of external pad use, the authors report satisfactory continence (2 less pads a day) by 88% of their patients.

Martins and Boyd (*British Journal of Urology*, 75, 354-358 (1995)) reported on 145 male patients who had AMS Sphincter 800™ Urinary Prosthesis implanted between January 1987 and November 1993. The mean follow up was 343 months (range 1-83). The authors report that infection/erosion occurred in 13 patients (9%). All 13 patients had undergone radical retropubic prostatectomy, radical cystectomy and abdomino-perineal resection. Seven patients had also received radiation therapy. Cuff placement was bulbar in all 13 patients. These authors conclude that, “despite all the precautions taken, there remains a group of patients who are still at a higher risk of infection-erosion due to adverse circumstances that distort the anatomy of the perineal area, impair the host defense mechanisms, and ultimately enable the establishment of the infection-erosion complex. Radiotherapy is known to increase the likelihood of nonmechanical complication, specifically infection-erosion”.

Light and Reynolds (*Journal of Urology*, 147, 609-611 (1992)) also reported on the impact of the cuff design changes in reducing complications. Mean follow-up for the narrow back cuff was 27 months. A total of 146 cuffs were implanted in 126 (88 male and 38 female) patients. The incidence of cuff leaks was 1.3%, while the overall revision rate for clinically significant pressure atrophy was 9%.

Montague (*Journal of Urology*, 147,380-382 (1992)) reported on the treatment of 166 patients (156 male and 10 female) with AMS Sphincter 800™ Urinary Prosthesis . One hundred and nineteen (119) male patients had either total prostatectomy or subtotal prostatectomy. Mean follow up was 41.6 months (range 6 to 94 months). A total of 40 reoperations (27 revisions and 13 device removals) were performed in 32 of the 166 patients (19.3%). There were 13 mechanical device failures (7.8%), 11 cuff erosions (6.6%) and 2 prosthesis infections (1.2%). Eighty-eight (48.8%) patients used no pads, 44 (26.5%) used one pad a day for “near total continence rate” of 75.3%. Eighteen (10.8%) more patients used 3 or less than 3 pads/day.

Kowalczyk et al. (*Journal of Urology*, 156, 1300-1301 (1996)) reported cuff erosion rate of 10.5% in men who received AMS Sphincter 800™ Urinary Prosthesis for their stress incontinence following prostatectomy. Their study involved 95 men of whom 90 received a double cuff (two cuffs). They conclude that addition of a second cuff to the artificial urinary sphincter remains a safe alternative for patients with severe urinary stress incontinence as pointed out by Brito et al. (*Journal of Urology*, 149, 283- (1993)) who implanted 15 patients with double cuff. Kabalin (*Journal of Urology*, 156, 1302-1304 (1996)) notes that stress urinary incontinence may persist in approximately 15% of men following implantation of a standard artificial urinary sphincter and recommends implantation of a second urethral cuff to provide satisfactory urinary continence in men with an artificial urinary sphincter and persistent incontinence. In Kowalczyk’s study,

the rate of socially acceptable dryness, as defined by Montague, remained greater than 95% in their patients with the double cuff sphincter.

Mottet et al. (*Urology International*, 60, *Supplement 2*, 25-29 (1998)) reported on 103 men who were implanted with AMS Sphincter 800™ Urinary Prosthesis for urinary incontinence following radical prostatectomy. The follow up ranged between 1 and 3 years. In these patients, 12% revisions were due to infection/erosion and 10% revisions were due to mechanical failures. Sixty one percent (59 patients) were dry and 28% (27 patients) had leakage of a few drops.

Heitz (*Journal of Urology*, Supplement 4, Abstract #1029 (1997)) reported on 321 male patients who suffered from iatrogenic incontinence due to radical prostatectomy. Thirty one (9.6%) patients had revisions due to mechanical (cuff leakage) problems and 64 (19.9%) patients had revisions for non-mechanical problems (45 for tissue atrophy, 11 for infection and cuff erosion and 8 had device removed permanently). The overall revision rate for mechanical and non-mechanical causes was 29.5%. Regarding benefits, 277 (86%) patients were completely dry or used 1 pad/day. Nineteen (6%) patients used 2-3 pads/day and 17 (5%) patients were treatment failures. The authors conclude that AMS Sphincter 800™ Urinary Prosthesis has proven to be a safe and reliable treatment option for post-prostatectomy incontinence.

Haab et al. (*Journal of Urology*, 158, 435-439 (1997)) reviewed the medical records of 68 male patients treated at their institution between March 1980 and March 1992. Sixty-four of the 68 patients had prostatectomy etiology. Mean follow-up was 7.2 years. In this group, 11 patients had revision surgery for mechanical complications and 10 patients had revisions for non-mechanical complications (urethral atrophy 6, urethral erosion 2, tubing erosion 1, permanent scrotal pain 1) for a total of 21 (31%) patients with revisions. Thirty-one (61%) patients were alive with functioning sphincter and satisfied after 10 years. Fifty-four (80%) patients were socially continent using 0-1 pad/day. Of the 52 patients who were available for long-term survey of quality of life, 88% percent of the patients would undergo treatment again and 85% would recommend treatment to a friend. The authors conclude that their long-term study documents the positive impact of the artificial urinary sphincter on patient quality of life with few mechanical failures.

Herschorn et al. (*Journal of Urology*, 155), *Abstract # 583 (May 1996)* reported on the treatment of 123 males and 11 females. Sixty-eight patients were post- radical prostatectomy patients and 32 were post-TURP. Not all but most patients received AMS Sphincter 800™ Urinary Prosthesis with new modifications, as they became available. Mean follow-up was 37.6 months. Forty-four (32.5%) patients required reoperations, 16 had more than one reoperation and 9 had the device removed permanently. In 15 (12.2%) patients, the revisions were due to device failure (mechanical problems). Non-mechanical problems accounted for revisions in 29 (23.5%) patients. Fifteen patients (12.2%) had reoperation for persistent incontinence and 14 (11.4%) had revisions due to infection and/or erosion. The radical prostatectomy group underwent fewer revisions (13/69=19%). Median survival of the device was 85.2 months.

Litwiller et al. (*Journal of Urology*, 156, 19775-1980 (1996)) reported on 65 male patients with AMS Sphincter 800™ Urinary Prosthesis for their post-prostatectomy incontinence over a period of 9 years. In this group of 65 patients, the revisions totaled 18%; 9% due to atrophy 6% due to infection and 3.1% due to erosion. For documenting patient satisfaction with the treatment, the authors were able to survey only 50 patients using telephone interview or written questionnaire. Mean follow-up was 23.4 months. The long-term complete continence rate was only 20%. Of the patients with wetness, 55% had leakage of a few drops daily and 22% had leakage of less than a teaspoon. These results indicate that 97% of the surveyed patients had acceptable continence. In the survey, a total of 90% of the patients reported satisfaction with the AMS Sphincter 800™ Urinary Prosthesis and 96% stated that they would recommend the device to a friend. Seven (14%) patients reported improved sexual activity.

Fleshner and Herschorn (*Journal of Urology*, 155, 1260-1263 (1996)) interviewed and also collected responses to a standard questionnaire regarding their activities of daily living and quality of life from 30 men who received AMS 800 sphincter following radical prostatectomy. They conclude that the artificial urinary sphincter is an effective form of therapy for post-radical prostatectomy incontinence but irritative voiding symptoms occur, which tend to limit activities of daily living. Since the authors state that these patients were implanted with the sphincter device during the last 14 years, not all patients would have received AMS Sphincter 800™ Urinary Prosthesis. Therefore, the irritative voiding symptoms may not be attributable to the modern AMS Sphincter 800™ Urinary Prosthesis model with narrow back cuff design introduced in 1987.

### **Risks versus Benefits**

There are some risks associated with AMS Sphincter 800™ Urinary Prosthesis implant. In addition to the risks involved with the surgical procedure to implant the device, several risks associated with the device have been documented in numerous publications over the years and in the 3 studies conducted by AMS. The rates of some risks, especially tissue erosion from cuff pressure have decreased after the introduction of the narrow back cuff design in 1987 and the use of a double cuff in some patients. Still the PIF Study, the Prospective Study and the Retrospective Study indicate the risks are not negligible as discussed earlier. The rates for various risks were: Infection 2.3- 6.7%; Erosion 2.4-16.2%, Fluid Loss 2.3-7.0%, Mechanical malfunction 0.66-10.6%, Migration 0.36-4.7%, Recurring incontinence 1.2-27.2%. Often these risks require operation.

Although the risks are not insignificant, the benefits of AMS Sphincter 800™ Urinary Prosthesis outweigh these risks for the intended use of treating urinary incontinence due to intrinsic sphincter deficiency following prostate surgery. The most important factors to be considered are: 1) the device is not the first choice but the last choice for the patients who have severe incontinence resulting from prostate surgery and 2) there is no other artificial sphincter device available in the market for these patients. The literature and the studies referenced in this PMA indicate that 65-70% of the patients achieve dryness, 90%

of the patients achieve reasonable improvement in their incontinence (up to 3 pads/day) and 90-95% of the patients expressed satisfaction with the device because it improved the quality of their lives.

## **XI. CONCLUSIONS DRAWN FROM STUDIES**

Preclinical studies assessed the device design, mechanical properties, reliability, and materials biocompatibility. Results from this testing provide assurance that the device design is appropriate for the intended use. The published literature as summarized above provides additional evidence to support the decision that the device is reasonably safe and effective for its intended use.

Results from the Prospective Study indicate that quality of life improved for patients treated with the AMS Sphincter 800™ Urinary Prosthesis, as measured by the Incontinence Impact Score and Rosenberg Self-Esteem Scale. Continence status also improved for most patients. After two years, physician assessment of continence was 73.3% of patients were completely or substantially dry and 23.3% only required some additional protection. Patients' assessment of continence was consistent with the physicians'. The estimated 5-year revision-free rate of 74%, based on hierarchical Bayesian model, is in close agreement with the data available in the PIF Study and published literature. The Prospective Study provided no additional information that affects the known safety and effectiveness profile of the device for this specific patient population.

## **XII. PANEL RECOMMENDATIONS**

The PMA was not referred to the Gastroenterology and Urology Devices Advisory Panel for review and recommendations since the device has been marketed for 17 years and extensive literature exists on the performance of the device.

## **XIII. CDRH DECISION**

Based on the information provided in the PMA, CDRH has determined that the AMS Sphincter 800™ Urinary Prosthesis is reasonably safe and effective for the indication of treatment of urinary incontinence due to reduced outflow resistance (intrinsic sphincter deficiency) following prostate surgery.

The device manufacturing facility of American Medical Systems and sterilization sites were inspected and found to be in compliance with the Quality System Regulation (21CFR 820).

## **XIV. APPROVAL SPECIFICATIONS**

: Labeling: See the Physician and Patient Brochures that are described below.

- AMS Sphincter 800™ Urinary Prosthesis, Package Insert
- AMS Sphincter 800™ Urinary Prosthesis, Operating Room Manual
- Patient Information and Instructions for the AMS Sphincter 800™ Urinary Prosthesis

Hazards to Health from Use of the Device:

See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.