

eliminates the unsafe condition; or different actions necessary to address the unsafe condition described in this AD. Such a request should include an assessment of the effect of the changed configuration on the unsafe condition addressed by this AD. In no case does the presence of any modification, alteration, or repair remove any airplane from the applicability of this AD.

Compliance: Required as indicated, unless accomplished previously.

To prevent reduced controllability of the airplane due to structural deformation in the elevator control system, accomplish the following:

(a) Within 6 months after August 10, 1994 (the effective date of AD 94-14-07, amendment 39-8959), modify the mounting structure of the elevator controls on the rear pressure bulkhead, in accordance with Jetstream Service Bulletin J41-53-012, dated November 30, 1993, or Revision 1, dated October 3, 1994.

(b) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, Standardization Branch, ANM-113, FAA, Transport Airplane Directorate. Operators shall submit their requests through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, Standardization Branch, ANM-113.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the Standardization Branch, ANM-113.

(c) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished. Issued in Renton, Washington, on February 9, 1995.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 95-3753 Filed 2-14-95; 8:45 am]

BILLING CODE 4910-13-U

14 CFR Part 39

[Docket No. 91-NM-195-AD]

Airworthiness Directives; Boeing Model 747-400 Series Airplanes

AGENCY: Federal Aviation Administration, DOT.

ACTION: Proposed rule; withdrawal.

SUMMARY: This action withdraws a notice of proposed rulemaking (NPRM) that proposed to supersede an existing airworthiness directive (AD), applicable to certain Boeing Model 747-400 series airplanes. That action would have required the modification of certain distance measuring equipment (DME), which would terminate a previously required limitation of the FAA-

approved Airplane Flight Manual (AFM) that prohibits terminal area and enroute area navigation operations under certain conditions. Since the issuance of the NPRM, the Federal Aviation Administration (FAA) has issued separate rulemaking that requires installation of the modification proposed in the NPRM. Accordingly, the proposed rule is withdrawn.

FOR FURTHER INFORMATION CONTACT: Pete Skaves, Aerospace Engineer, Systems and Equipment Branch, ANM-130S, FAA, Transport Airplane Directorate, Seattle Aircraft Certification Office, 1601 Lind Avenue, SW., Renton, Washington 98055-4056; telephone (206) 227-2795; fax (206) 227-1181.

SUPPLEMENTARY INFORMATION: A proposal to amend part 39 of the Federal Aviation Regulations (14 CFR part 39) to supersede AD 91-12-08, amendment 39-7019 (56 FR 25362, June 4, 1991), applicable to certain Boeing Model 747-400 series airplanes, was published in the **Federal Register** on November 1, 1991 (56 FR 56177). The proposed rule would have required modification of certain distance measuring equipment (DME). Accomplishment of that modification would have constituted terminating action for a previously required limitation of the FAA-approved Airplane Flight Manual (AFM) that prohibits terminal area and enroute area navigation operations under certain conditions. That action was prompted by the development of a design change that would prevent erroneous distance information from being displayed to the flight crew and sent to the flight management computer (FMC). The proposed actions were intended to prevent decreased enroute area navigation (RNAV) accuracy or decreased terminal area navigation capabilities, which may then necessitate missed approaches, the use of alternative means of navigation for approach, or diversion to an alternative airport.

Since the issuance of that NPRM, the FAA issued AD 94-02-02 (59 FR 2519, January 18, 1994), applicable to Rockwell International/Collins Air Transport Division DME-700 Distance Measuring Equipment. (A correction of the rule was published in the **Federal Register** on February 23, 1994 (59 FR 8519)). That AD requires, in part, modification of certain DME units, including those units installed on the Boeing Model 747-400 series airplanes that would have been applicable to the rule proposed by the NPRM.

Since modification of the DME units is now required by AD 94-02-02, the FAA finds that the proposed

requirements of the NPRM are unnecessary, since they would merely duplicate those currently required by AD 94-02-02. Accordingly, the proposed rule is hereby withdrawn.

Additionally, since the modification required by AD 94-02-02 eliminates the need for the AFM limitation required by AD 91-12-08, the FAA is considering rescinding that AD by a separate rulemaking action.

Withdrawal of this notice of proposed rulemaking constitutes only such action, and does not preclude the agency from issuing another notice in the future, nor does it commit the agency to any course of action in the future.

Since this action only withdraws a notice of proposed rulemaking, it is neither a proposed nor a final rule and therefore, is not covered under Executive Order 12866, the Regulatory Flexibility Act, or DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979).

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Withdrawal

Accordingly, the notice of proposed rulemaking, Docket 91-NM-195-AD, published in the **Federal Register** on November 1, 1991 (56 FR 56177), is withdrawn.

Issued in Renton, Washington, on February 9, 1995.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 95-3751 Filed 2-14-95; 8:45 am]

BILLING CODE 4910-13-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 876

[Docket No. 94N-0380]

Gastroenterology-Urology Devices; Effective Date of the Requirement for Premarket Approval of the Implanted Mechanical/Hydraulic Urinary Continence Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; opportunity to request a change in classification.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the filing of a premarket approval application (PMA) or a notice

of completion of a product development protocol (PDP) for the implanted mechanical/hydraulic urinary continence device, a medical device. The agency is also summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the statute's approval requirements, and the benefits to the public from the use of the device. In addition, FDA is announcing an opportunity for interested persons to request that the agency change the classification of the device based on new information.

DATES: Written comments by June 15, 1995; requests for a change in classification by March 2, 1995. FDA intends that, if a final rule based on this proposed rule is issued, PMA's will be required to be submitted within 90 days of the effective date of the final rule.

ADDRESSES: Submit written comments or requests for a change in classification to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John H. Baxley, or John F. Guest, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-2194.

SUPPLEMENTARY INFORMATION:

I. Background

Section 513 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c) requires the classification of medical devices into one of three regulatory classes: Class I (general controls), class II (special controls), and class III (premarket approval). Generally, devices that were on the market before May 28, 1976, the date of enactment of the Medical Device Amendments of 1976 (the amendments) (Pub. L. 94-295), and devices marketed on or after that date that are substantially equivalent to such devices, have been classified by FDA. For the sake of convenience, this preamble refers to both the devices that were on the market before May 28, 1976, and the substantially equivalent devices that were marketed on or after that date as "preamendments devices."

Section 515(b)(1) of the act (21 U.S.C. 360e(b)(1)) establishes the requirement that a preamendments device that FDA has classified into class III is subject to premarket approval. A preamendments class III device may be commercially distributed without an approved PMA or declared completed PDP until 90 days after FDA's promulgation of a final

rule requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the act, whichever is later. Also, a preamendments device subject to the rulemaking procedures under section 515(b) of the act is not required to have an approved investigational device exemption (IDE) (part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final rule requiring the submission of a PMA for the device.

Section 515(b)(2)(A) of the act provides that a proceeding to promulgate a final rule to require premarket approval shall be initiated by publication, in the **Federal Register**, of a notice of proposed rulemaking containing: (1) The proposed rule; (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA or declared completed PDP and the benefit to the public from the use of the device; (3) an opportunity for the submission of comments on the proposed rule and the proposed findings; and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(2)(B) of the act provides that if FDA receives a request for a change in the classification of the device within 15 days of the publication of the notice, FDA shall, within 60 days of the publication of the notice, consult with the appropriate FDA advisory committee and publish a notice denying the request for change of classification or announcing its intent to initiate a proceeding to reclassify the device under section 513(e) of the act. If FDA does not initiate such a proceeding, section 515(b)(3) of the act provides that FDA shall, after the close of the comment period on the proposed rule and consideration of any comments received, promulgate a final rule to require premarket approval, or publish a notice terminating the proceeding. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the act, unless the reason for termination is that the device is a banned device under section 516 of the act (21 U.S.C. 360f).

If a proposed rule to require premarket approval for a preamendments device is made final, section 501(f)(2)(B) of the act (21 U.S.C. 351(f)(2)(B)) requires that a PMA or notice of completion of a PDP for any such device be filed within 90 days of the date of promulgation of the final

rule or 30 months after final classification of the device under section 513 of the act, whichever is later. If a PMA or notice of completion of a PDP is not filed by the later of the two dates, commercial distribution of the device is required to cease. The device may, however, be distributed for investigational use if the manufacturer, importer, or other sponsor of the device complies with the IDE regulations. If a PMA or notice of completion of a PDP is not filed by the later of the two dates, and no IDE is in effect, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the act, and subject to seizure and condemnation under section 304 of the act (21 U.S.C. 334) if its distribution continues. Shipment of the device in interstate commerce will be subject to injunction under section 302 of the act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the act (21 U.S.C. 333). FDA has in the past requested that manufacturers take action to prevent the further use of devices for which no PMA or notice of completion of a PDP has been filed and may determine that such a request is appropriate for implanted mechanical/hydraulic urinary continence devices.

The act does not permit an extension of the 90-day period after promulgation of a final rule within which an application or a notice is required to be filed. The House Report on the amendments states that "the thirty month 'grace period' afforded after classification of a device into class III * * * is sufficient time for manufacturers and importers to develop the data and conduct the investigations necessary to support an application for premarket approval." (H. Rept. 94-853, 94th Cong., 2d sess. 42 (1976).)

A. Classification of the Implanted Mechanical Hydraulic Urinary Continence Device

In the **Federal Register** of November 23, 1983 (48 FR 53012 at 53026), FDA issued a final rule classifying the implanted mechanical/hydraulic urinary continence device into class III § 876.5280 (21 CFR 876.5280). The preamble to the proposal to classify the device (46 FR 7610, January 23, 1981) included the recommendation of the Gastroenterology-Urology Devices Advisory Panel (the Panel), an FDA advisory committee, which met on September 26 and 27, 1976, regarding the classification of the device. The Panel recommended that the device be in class III, and identified certain risks to health presented by the device. FDA agreed with the Panel's

recommendation and proposed that the implanted mechanical/hydraulic urinary continence device be classified into class III. The proposal stated that the agency believed that general controls and performance standards are insufficient to provide reasonable assurances of the safety and effectiveness of the device and that there is insufficient information to establish a standard to provide reasonable assurances of the safety and effectiveness of the device. The proposal stated that premarket approval is necessary for this device because it presents a potential unreasonable risk of injury due to: (1) Adverse tissue reaction and erosion; (2) leakage of urine secondary to device defects; (3) infection resulting from defects in the design, construction, packaging, or processing of the device; (4) urinary tract infection, secondary to urine stasis, occurring as a result of the inflation cuff locking in the closed position; and (5) additional surgery that might be required as a result of a malfunction of the device. In support of its proposal to strengthen regulatory surveillance of the device, FDA cited references supporting the proposed classification.

The preamble to the November 23, 1983, final rule (48 FR 53012) classifying the device into class III advised that the earliest date by which PMA's for the device could be required was June 30, 1986, or 90 days after promulgation of a rule requiring premarket approval for the device, whichever occurs later. In the **Federal Register** of January 6, 1989 (54 FR 550), FDA published a notice of intent to initiate proceedings to require premarket approval of 31 preamendments class III devices assigned a high priority by FDA for the application of premarket approval requirements. Among other things, the notice described the factors FDA takes into account in establishing priorities for proceedings under section 515(b) of the act for promulgating final rules requiring that preamendments class III devices have approved PMA's. Although the implanted mechanical/hydraulic urinary continence device was not listed among these 31 devices, the agency has received more than 2,700 medical device reports (MDR's) since 1984 for this device. Additionally, the types of problems identified in these reports are similar to those identified during the classification proceedings of the device. Therefore, FDA has determined that the implanted mechanical/hydraulic urinary continence device identified in § 876.5280 has a high priority for

initiating a proceeding to require premarket approval. Accordingly, FDA is commencing a proceeding under section 515(b) of the act to require that the implanted mechanical/hydraulic urinary continence device has an approved PMA or a declared completed PDP.

B. Dates New Requirements Apply

In accordance with section 515(b) of the act, FDA is proposing to require that a PMA or a notice of completion of a PDP be filed with the agency for the implanted mechanical/hydraulic urinary continence device within 90 days after promulgation of any final rule based on this proposal. An applicant whose device was legally in commercial distribution before May 28, 1976, or has been found by FDA to be substantially equivalent to such a device, will be permitted to continue marketing the implanted mechanical/hydraulic urinary continence device during FDA's review of the PMA or notice of completion of the PDP. FDA intends to complete the review of any PMA for the device within 180 days and a notice of completion of a PDP within 90 days of the date of filing. FDA cautions that, under section 515(d)(1)(B)(i) of the act, FDA may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the agency finds that " * * * the continued availability of the device is necessary for the public health."

FDA intends that, under § 812.2(d), the preamble to any final rule based on this proposal will state that, as of the date on which a PMA or notice of completion of a PDP is required to be filed, the exemptions in § 812.2(c)(1) and (c)(2) from the requirements of the IDE regulations for preamendments class III devices will cease to apply to any implanted mechanical/hydraulic urinary continence device which is: (1) Not legally on the market on or before that date, or (2) legally on the market on or before that date but for which a PMA is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA or notice of completion of a PDP for the implanted mechanical/hydraulic urinary continence device is not filed with FDA within 90 days after the date of promulgation of any final rule requiring premarket approval for the device, commercial distribution of the device must cease. The device may be distributed for investigational use only if the requirements of the IDE regulations regarding significant risk devices are met. The requirements for significant risk devices include submitting an IDE application to FDA

for its review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued. FDA, therefore, cautions that IDE applications should be submitted to FDA at least 30 days before the end of the 90-day period after the final rule to avoid interrupting investigations.

C. Description of the Device

An implanted mechanical/hydraulic urinary continence device is a device used to treat urinary incontinence by the application of continuous or intermittent pressure to occlude the urethra. The totally implanted device may consist of either a static pressure pad, or a system with a container of saline or radiopaque fluid in the abdomen and a manual pump and valve under the skin surface that is connected by tubing to an adjustable pressure pad or to a cuff around the urethra. The fluid is pumped as needed from the container to inflate the pad or cuff to compress the urethra. These devices are most commonly constructed from silicone elastomers. Additionally, static pressure pad designs have been known to contain silicone gel and/or polyurethane foam covering.

The proposed rule to require premarket approval of implanted mechanical/hydraulic urinary continence devices applies to legally marketed implanted mechanical/hydraulic urinary continence devices identified above that were commercially distributed before May 28, 1976, and to devices introduced into commercial distribution since that date that have been found to be substantially equivalent to such implanted mechanical/hydraulic urinary continence devices.

D. Proposed Findings With Respect to Risks and Benefits

As required by section 515(b) of the act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring the implanted mechanical/hydraulic urinary continence device to have an approved PMA or a declared completed PDP; and (2) the benefits to the public from the use of the device.

E. Degree of Risk

After considering the information discussed by the Panel during the classification proceedings, as well as the published literature and MDR's, FDA has evaluated the risks associated with the implanted mechanical/hydraulic urinary continence device. FDA now believes that the following are

significant risks associated with the use of the implanted mechanical/hydraulic urinary continence device:

1. Erosion of the Implanted Mechanical/Hydraulic Urinary Continence Device

Erosion is the destruction or breakdown of tissue and is the most common cause of failure in the implanted mechanical/hydraulic urinary continence device (Refs. 1 through 5). Cuff erosion into the urethra or bladder neck is a serious complication that has been frequently reported (Refs. 3 and 6 through 15). This type of erosion makes reimplantation difficult and is associated with higher complication rates for reimplantation (Refs. 1 and 16 through 18) of the device. Erosion of the pump through the labia, vagina, scrotum (Refs. 14 and 19 through 21), and the perineum (Refs. 2, 9, and 22) have also been reported.

Erosion often occurs as a result of low grade, nonclinical infection of the prosthesis (Refs. 9, 14, and 23 through 28). Other factors which can contribute to erosion include previous surgery (Ref. 11), poor vascularization (Refs. 27 and 29 through 31), prior pelvic irradiation (Refs. 17, 28, and 32 through 35), improper cuff size (Ref. 30), improper reservoir volume (Ref. 17), surgical injury (Refs. 18 and 24), excessive urethral compression (Ref. 16), and premature activation (Refs. 19 and 27).

2. Infection

Infection, a risk of any surgical implant procedure, is associated with the use of implanted mechanical/hydraulic urinary continence devices (Refs. 7, 10, 12, 33, and 36 through 39). Infection is one of the most serious potential complications of device implantation and usually necessitates removal of the prosthesis (Refs. 7, 40, and 41). As in any implantation procedure, compromised device sterility and/or surgical techniques may be major contributing factors to this risk (Refs. 40 and 42). Additionally, a life-long risk for hematogenously seeded infection possibly exists in these patients and antibacterial prophylaxis for subsequent dental and surgical procedures may be needed (Ref. 40).

3. Mechanical Malfunctions

Fluid leakage is one of the most commonly reported mechanical malfunctions (Refs. 2, 26, 28, 37, 43, and 44) of implanted mechanical/hydraulic urinary continence devices. Fluid can leak from the cuff or pad (Refs. 7, 13, 21, 31, and 45), reservoir (Refs. 7, 13, and 31), or connectors (Ref. 10). Leakage from the cuff has been associated with cuff folding and attendant material wear

(Refs. 31, 36, and 46). This malfunction results in inadequate cuff pressure and incontinence (Ref. 7). Tube kinking is another reported device malfunction (Refs. 7, 12, 26, 28, 34, 37, 43, 44, and 47). Also, disconnection of the tubing from components of the device can occur (Ref. 19). Pump assembly failure is another noted complication (Refs. 2, 19, 36, 37, and 44) of this implant. This can include malfunction of the valves within the hydraulic system (Ref. 45). Finally, balloon herniation has been noted (Ref. 17). Device malfunction usually requires replacement or revision surgery (Refs. 7 and 43).

4. Iatrogenic Disorders

Iatrogenic complications can occur as a result of any medical procedure, including implantation of the implanted mechanical/hydraulic urinary continence device. Improper device handling (including cutting or nicking of the device) can lead to device malfunctions. Inadequate pressure within the system (due to selection of incorrect cuff or reservoir size) results in either incontinence (due to inadequate urethral closing pressure) or outflow obstruction (due to excessive urethral closing pressure), both of which lead to the need for reoperation (Refs. 7, 12, 30, and 34). This may be due to a lack of guidance for determining the appropriate device size for an individual patient (Refs. 2, 9, 25, 31, and 48). Erosion secondary to infection, can be caused by intraoperative field contamination or urethral or vaginal injury (Refs. 26 and 42). Finally, intraoperative and postoperative kinks in the tubing can occur due to incorrect tubing length (Ref. 7) and result in a low urethral closure pressure (Refs. 9, 34, and 48).

5. Hydronephrosis

Hydronephrosis refers to the dilation of the upper urinary tract as a result of chronic obstruction to urine outflow, which can lead to kidney damage. Some authors have reported an elevated incidence of hydronephrosis following implantation of the implanted mechanical/hydraulic urinary continence device (Refs. 49 through 52). This complication has mostly occurred when the device is implanted in patients with myelopathy. It has been theorized that the development of hydronephrosis is due to a combination of slight detrusor hyperreflexia and low bladder capacity (Ref. 49). Other researchers have noted the development of detrusor hypertonicity after implantation, leading to hydronephrosis (Ref. 52). The pathogenesis and

incidence of this risk is unknown and requires further study.

6. Human Carcinogenicity

Carcinogenesis has been widely discussed as a reputed risk secondary to implantation of any material. Evidence from the literature indicates that in animal studies, different forms of silicone have been associated with various types of cancer (Refs. 53 through 57). Cases of several types of cancer in humans have been reported in association with various forms of implanted silicone (Refs. 58 through 61).

7. Human Reproductive and Teratogenic Effects

The effect of certain silicone compounds on the reproductive potential of the male is largely unknown. Le Vier and Jankowiak report that at least one form of organosiloxane, which is known to be present in some silicone gels, mimics estrogens in the male rat, leading to rapid testicular atrophy (Ref. 62).

Teratogenesis includes the origin or mode of production of a malformed fetus and the disturbed growth processes involved in the production of a malformed fetus. Studies using silicone fluid in animals have been minimal, and yield contradictory and inconclusive results (Refs. 63 through 65). Prolonged contact with either silicone elastomer, or silicone gel-filled membrane in devices containing silicone gel, presents a potential risk of teratogenicity in humans. Further study of these risks is necessary.

8. Immune Related Connective Tissue Disorders—Immunological Sensitization

Immunological sensitization may be a serious risk associated with an implanted mechanical/hydraulic urinary continence device. Recent clinical data have shown that silicone elastomers are capable of producing immune responses (Ref. 66). Immune related connective tissue disorders have also been reported in women who have silicone gel-filled devices or who have had silicone injections in augmentation mammoplasty. There are clinical reports of several patients who have undergone augmentation mammoplasty with silicone gel-filled breast prostheses and later presented with connective tissue disease-like syndromes (Ref. 67). Recently, Naim et. al. conducted studies in rats which demonstrated that silicone gel is a potent immunological adjuvant (Ref. 68). Because implanted mechanical/hydraulic urinary continence devices may consist of similar silicone elastomers and gels,

further study of the potential risk of immune related connective tissue disorders in humans with these implants is warranted.

9. Biological Effects of Silica

Amorphous (fumed) silica is bound to the silicone in the elastomer of the implanted mechanical/hydraulic urinary continence device, and may be fibrogenic and immunogenic. Fumed silica and the silicone elastomer each elicit cellular responses in rats (Ref. 69). Researchers have reported that there is an association between industrial exposure to silica and development of systemic lupus erythematosus (Ref. 41). The biological effects of silica, particularly the immunologic component of these reactions, present a potential risk for device recipients and need to be examined.

10. Silicone Particle Shedding, Silicone Gel Leakage, and Associated Migration

Silicone particle shedding and subsequent migration have been reported with genitourinary prosthetic devices, including implanted mechanical/hydraulic urinary continence devices (Refs. 70 and 71). Silicone gel leakage and migration from the silicone elastomer envelope, either from rupture of the envelope or by leaking of the gel through the envelope (gel "bleed"), are also potential significant risks of implanted mechanical/hydraulic urinary continence devices containing silicone gel. Rupture of the envelope with gel leakage and subsequent migration may be secondary to surgical technique, or may result from mechanical stresses such as device usage, trauma, and wear on the envelope, and necessitates removal of the implant. In addition, silicone gel-filled breast implants are reported to "bleed" micro amounts of silicone through the intact silicone elastomer shell into the surrounding tissues (Refs. 72 through 81). Furthermore, fluorosilicone gels have been used to lubricate the inner surfaces of cuff shells (Ref. 36) and, therefore, are an additional source for gel bleed. Although diffusion of silicone gel through the elastomer envelope and silicone particle shedding have not specifically been measured (e.g., quantified) in the implanted mechanical/hydraulic urinary continence device, they have been reported (Ref. 70) and, therefore, particle shedding and gel bleed continue to be potential risks with this device and need to be evaluated. Migration of the particles and gel into the human body presents the potential for development of adverse effects such

as granulomas, lymphadenopathy, or cellular immune response (Refs. 41, 58, 59, 70, and 71). The ultimate fate of migrating silicone particles or silicone gel within the body is currently not well understood. It should be noted that the use of silicone gel in these devices may have been discontinued.

11. Degradation of Polyurethane Elastomer

Polyurethane elastomer materials, which may be present in some implanted mechanical/hydraulic urinary continence devices, may degrade over time and release degradation products such as methylene diamine or toluene diamine, which are potential carcinogens in animals (Refs. 82 and 83). FDA is not aware of any mechanical/hydraulic urinary continence devices which currently use this material. This potential risk is associated only with those implanted mechanical/hydraulic urinary continence devices that contain polyurethane elastomers.

12. Degradation of Polyurethane Foam

This potential risk is associated only with those implanted mechanical/hydraulic urinary continence devices that are covered with polyurethane foam. The polyurethane foam material that has been used to cover some devices is known to degrade over time with a potential breakdown product of 2,4 diaminotoluene (TDA), a known carcinogen in animals (Refs. 84 through 89). The fate of the degraded product in vivo is unknown to date, and the use of this material in implanted mechanical/hydraulic urinary continence devices may have been discontinued. Case reports of polyurethane foam covered silicone gel-filled breast implants indicate that there is greater difficulty with the removal of this type of prosthesis due to fragmented polyurethane shell and/or capsular tissue ingrowth (Refs. 90 through 96). Also, foreign body response has been reported concurrent with the use of the polyurethane foam covered testicular prosthesis in humans (Ref. 97).

13. Other Reported Complications

The following are among the additional risks which have also been reported with the implanted mechanical/hydraulic urinary continence device: perineal discomfort/pain (Refs. 10, 17, and 27); development of bladder hyperreflexia (Refs. 98 through 100); worsening/persistence of incontinence (Refs. 51, 99, and 100); urinary retention (Refs. 51 and 101); hematoma (Ref. 28); seroma (Ref. 44); inguinal hernia formation (Ref. 102);

fibrous capsule formation, failure of cuff to deflate, broken tubing (Ref. 51); fistula formation from urethral erosion (Ref. 8); urethral scarring (Ref. 99); bleeding (Ref. 103); urethral stricture requiring urethrotomy (Ref. 101); wound dehiscence, pelvic abscess (Ref. 104); and fistula to the skin (Ref. 10).

F. Benefits of the Device

The implanted mechanical/hydraulic urinary continence device is intended to provide intermittent or continuous pressure to occlude the urethra, thereby restoring urinary continence. The device is indicated in males or females whose urinary sphincter is dysfunctional.

Implants have been used to treat incontinence resulting from prostatectomy, myelopathy (e.g., spina bifida, myelomeningocele), spinal column injury, sacral agenesis/dysgenesis, exstrophy/epispadias syndrome, pelvic trauma, and other conditions.

Although there are adverse physiologic effects associated with urinary incontinence (e.g., infection and skin irritation due to exposure to urine) (Ref. 105), the incontinent patient's mental health and quality of life can also suffer significantly. Incontinence can be socially, psychologically, and physically debilitating (Refs. 43 and 106). A reduction of social activities and interactions can be associated with the loss of urinary continence (Ref. 105). The loss of self-esteem (Ref. 107) and emotional problems (Ref. 25) have also been associated with this condition. Finally, some research has shown a relationship between depression indices and incontinence (Ref. 105).

An implanted mechanical/hydraulic urinary continence device can restore continence and may improve quality of life. Published studies indicate a moderately high success rate for either restoring or improving continence. Some of these studies have also noted that the restoration of continence can improve quality of life (Refs. 20 and 38) and self-esteem (Ref. 26).

G. Need for Information for Risk/Benefits Assessment of the Device

As the above sections indicate, there is reasonable identification of the risks and benefits associated with the implanted mechanical/hydraulic urinary continence device. There is, however, insufficient valid scientific evidence to permit FDA to perform a risk/benefit analysis. Therefore, FDA is now seeking further information on the following safety and effectiveness issues associated with the implanted mechanical/hydraulic urinary continence device:

(1) Long-term safety and effectiveness data for the device are needed. The incidence of implant failure and attendant causes, as well as the incidence of reoperations required, have not been clearly determined. Such device failures include, but are not limited to: Tissue erosion, infection, pain/discomfort, injury to the upper urinary tract due to either urinary retention or hydronephrosis, continued or worsened incontinence secondary to implantation of the implanted mechanical/hydraulic continence device, leakage, wear, tubing kinking/breaking or disconnection, pump failure, and cuff or pad failure. Also, the incidence rates of hematoma, seroma, inguinal hernia formation, fibrous capsule formation, fistula formation from urethral erosion, urethral scarring, bleeding, urethral stricture, development of bladder hyperreflexia, wound dehiscence, pelvic abscess, and fistula to the skin are poorly understood and need to be studied. Particularly, it is not well known whether the increased urethral resistance afforded by implanted mechanical/hydraulic urinary continence devices eventually leads to chronic upper urinary tract damage (e.g., hydronephrosis and/or worsening of renal function). This risk is especially a concern for young patients, who are most likely to have the device in place for many years.

(2) It is unknown for which subgroups of the population with urinary incontinence the benefits of the implanted mechanical/hydraulic continence device outweigh the attendant risks, especially since other voiding abnormalities, such as bladder dysfunction (detrusor instability and poor compliance) and reflux often coexist with sphincteric insufficiency. Factors which may increase the rate of complications include the etiology and duration of incontinence, age, gender, concomitant medical conditions, various anatomical abnormalities, patient motivation and manual dexterity, and prior treatments for the disorder, including prior surgery. An appropriate risk/benefit analysis is needed for each subgroup for whom the device will be indicated.

(3) The required presurgical workup of patients prior to device implantation, including the diagnostic tests to demonstrate significant sphincteric insufficiency which could be treated with the prosthesis, must be clarified. In particular, the proper patient selection and screening processes need to be developed and studied. Since some adverse events, such as persistent urinary incontinence, may be associated with other coexisting urodynamic

abnormalities (e.g., bladder dysfunction), these abnormalities must be effectively diagnosed prior to device implantation (Refs. 7, 22, and 108). The increased risk of hydronephrosis among device recipients whose bladders are unable to store urine at low pressures underscores the importance of thorough preoperative patient evaluation with special attention to bladder function and urodynamics (Ref. 103). Additionally, because the adverse events that may occur following implantation of the device may not be reversible, investigation is needed to determine which prior conservative therapies a patient should have failed before being considered an appropriate candidate for an implanted mechanical/hydraulic continence device.

(4) The long-term effects of devices implanted in pediatric patients need to be investigated. Currently, the relationship between patient growth and the need for implanted mechanical/hydraulic continence device revision or replacement is poorly understood and warrants further study. While some researchers report no effects related to the growth of the child, others report the potential for an effect upon both the growth/morphology of the organs in the urinary tract, as well as sexual development and function in children (Refs. 24 and 109).

(5) The effects of the implanted mechanical/hydraulic continence device upon male sexual function are poorly understood. In particular, the effect of the device upon erectile function needs to be examined.

(6) Since women of childbearing age are among the recipients of implanted mechanical/hydraulic continence devices, the effects of the device upon sexual function, pregnancy, and delivery must be analyzed.

(7) The effect of device implantation upon future medical diagnoses and treatments needs to be examined. Currently, it is not well understood whether the device's presence interferes with the ability to diagnose and treat disorders affecting the organs or structures in proximity to the implant components.

(8) The potential risks associated with silicone particle shedding and silicone gel leakage, and the subsequent migration of the particles and gel, need further clarification. This would include consideration of gel cohesiveness, envelope thickness/strength, gel bleed, and the role that the physical, mechanical, and chemical characteristics of silicone elastomers and gels play in the immediate or long-term wear of implanted mechanical/hydraulic urinary continence devices.

(The agency's concerns regarding silicone gel relate specifically to devices with gel-filled components, such as certain models of the implanted static pressure pad.)

(9) The potential long-term adverse effects of implanted mechanical/hydraulic urinary continence devices, such as cancer, immune related connective tissue disorders, and reproductive and teratogenic effects, are unknown. Likewise, in polyurethane elastomer and/or polyurethane foam covered implanted mechanical/hydraulic urinary continence devices (known to be applicable to certain models of the implanted static pressure pad), the long-term effects of the polyurethane material (such as mechanical integrity and carcinogenicity) are not understood. The agency notes that neither the silicone particles, which may shed from the device (Refs. 70, 110, and 111), nor the chemical forms of silicone monomers and oligomers, or additives (including catalysts, antioxidants, fillers, reinforcers, and other processing agents), which may leach from the device, have been characterized, and their metabolic fates are not known (Ref. 64). Furthermore, no satisfactory independent study has thoroughly evaluated the chronic long-term toxicity of silicone elastomers and their derivatives. Because children are among the potential recipients of these implants, information regarding the chronic toxic effects, including possible reproductive and teratogenic effects, of silicone could be of substantial importance in determining the risk to these patients and their offspring.

(10) The malfunction rate and longevity reported for implanted mechanical/hydraulic urinary continence devices have generally not reflected the predictions of preclinical testing. Further investigation is warranted to determine how the laboratory and animal studies can be designed to more accurately predict device reliability under actual conditions of use.

FDA believes, therefore, that the implanted mechanical/hydraulic urinary continence device should undergo premarket approval to obtain valid scientific evidence in order for FDA to determine whether the risks of using the device are adequately balanced by its benefits.

II. PMA Requirements

Any PMA for the device must include the information required by section 515(c)(1) of the act and the implementing provisions under 21 CFR 814.20. Such a PMA shall include a

detailed discussion, accompanied by the results of applicable preclinical and clinical studies, of the above identified risks and the effectiveness of the device. In particular, the PMA shall include all known or otherwise available data and other information regarding: (1) Any risks known or should be reasonably known to the applicant that have not been identified in this document; and (2) the effectiveness of the specific implanted mechanical/hydraulic urinary continence device that is the subject of the application.

Valid scientific evidence, as defined in § 860.7 (21 CFR 860.7), addressing the safety and effectiveness of the device should be presented, evaluated and summarized in a section or sections of the PMA separate from known or otherwise available safety and effectiveness information that does not constitute valid scientific evidence (e.g., isolated case reports, random experiences, etc.).

A. Manufacturing Information

All manufacturing information for the device should be completely described. The information should include but, is not necessarily limited to, the chemical formulation and manufacturing procedures and processes, presented in a step-by-step manner from the starting materials to the finished product, including, but not limited to, all nonreactants (such as antioxidants, light stabilizers, plasticizers, i.e., anything added to polymer resins that is necessary for processing of the finished product) and reactants (including catalysts, curing agents, and intermediate precursors) for the pad (including polyurethane foam covering, if applicable), cuff, pump, reservoir, tubing, and all internal components, adhesives, colorants, lubricants, and filling agents (e.g., gel, saline, contrast medium, etc.). A complete master list of the common chemical names and alternate names (manufacturer's trade name or code) for all nonreactants, reactants (including intermediate precursors), additives, catalysts, adjuvants, and products should be provided.

Chemical characterization of the elastomer intermediates (i.e., network precursors) of the pad (including polyurethane foam covering, if applicable), cuff, pump, reservoir, tubing, and internal gel (if applicable) sufficient to demonstrate control of the chemical processing of the device materials should be provided. This should be based on lot-to-lot comparisons (10 consecutive lot minimum) of the following information: (1) The molecular weight distribution,

expressed as weight average molecular weight, number average molecular weight, peak molecular weight, polydispersity, and viscosity average molecular weight of these precursors; (2) analyses for volatile and nonvolatile (if applicable) compounds, such as cyclic oligomers; (3) when viscosity is used as the variable that is measured for production control, a comparison of viscosity, number average molecular weight, and volatile content; and (4) isocyanate content, acidity, isomer ratios, hydroxyl number, water content, acid number, and peroxide content (where applicable). Documentation establishing the extent of cross-linking (where applicable) in the materials of the pad, cuff, pump, reservoir, tubing, and all internal components and filling agents, or the silicone-hydride and vinyl content of cross-linked materials of the pad, cuff, pump, reservoir, tubing, and all internal components and filling agents, as well as the particle size and surface area of the silica if present in the pad, cuff, pump, reservoir, tubing, and the composition of all internal components, filling agents, or gel should be provided. A complete description of the medium used to inflate the device (saline, contrast medium, etc.) and whether and how the implant will be prefilled must also be provided.

The standard operating procedures for sterility and materials qualifications must be provided. Sterilization information should include the method of sterilization; the detailed sterilization validation protocol and results; the sterility assurance level; the type of packaging; the packaging validation protocol and results; residual levels of ethylene oxide, ethylene glycol, and ethylene chlorohydrin remaining on the device after the sterilization quarantine period, if applicable; and the radiation dose, if applicable.

A complete description of the functional testing of subassemblies and finished products performed during the manufacturing process and during quality assurance/quality control (QA/QC) testing must be provided. Functional testing performed during manufacturing and QA/QC procedures should detect any device flaws that could lead to short-term failure and should demonstrate functional integrity of the device. A QA/QC plan that demonstrates how raw materials, components, subassemblies, and any filling agents will be received, stored, and handled in a manner designed to prevent damage, mixup, contamination, and other adverse effects must be provided. This plan shall specifically include, but not necessarily be limited to, a record of raw material, component,

subassembly, and filling agent acceptance and rejection, visual examination for damage, and inspection, sampling and testing for conformance to specifications.

Written procedures for finished device inspection to assure that device specifications are met must be provided. These procedures shall include, but are not limited to, the requirement that each production run, lot or batch be evaluated and, where necessary, tested for conformance with device specifications prior to release for distribution. A representative number of samples shall be selected from a production run, lot or batch and tested under simulated use conditions and to any extremes to which the device may be exposed.

Furthermore, the QA/QC procedures must include appropriate visual testing of the packaging, packaging seal, and product. Sampling plans for checking, testing, and release of the device shall be based on an acceptable statistical rationale (21 CFR 820.80 and 820.160).

B. Preclinical Data

Complete identification and quantification of all chemicals, including residual amine containing components, volatile and nonvolatile silicone cyclics and oligomers below a molecular weight of 1,500 exhaustively extracted from each of the individual structural components (pad, cuff, pump, reservoir, tubing, and any other materials, lubricants, or filling agents) as they are found in the final sterilized device should be reported. The solvents used for extraction should have varying polarities and should include, but not be limited to, ethanol/saline (1:9) and dichloromethane. Other, more contemporary extraction techniques, such as supercritical fluid extraction, may also be useful, at least for exhaustive extraction of the silicone materials. Experimental evidence must be provided establishing that exhaustive extraction is achieved with one of the selected solvents, and the percent recovery, especially for the more volatile components, must be reported. Extracts that may contain oligomeric or polymeric species must have the molecular weight distribution provided along with the number and weight average molecular weight, and polydispersity. All experimental methodologies must be described, and raw data (including instrument reports) must be provided along with all chromatographs, spectrograms, etc. The limit of detection (two times noise level) must be provided when the analyte of interest is not detected. Laboratory test methods and animal experiments used

in the characterization of the physical, chemical (other than exhaustive extraction) and mechanical properties of the device should be applicable to the intended use of the device in humans. Infrared measurements of the surface of device components as they occur in the final, sterilized product should be provided.

Biocompatibility testing data must be provided for all materials (pad, cuff, pump, reservoir, tubing, filling agents, gels, lubricants, and any other materials) in the implanted mechanical/hydraulic urinary continence device, including all color additives (ink, dyes, markings, etc.) used to fabricate the implanted mechanical/hydraulic urinary continence device. FDA guidance on biocompatibility testing is available in the document titled "Tripartite Biocompatibility Guidance for Medical Devices." A copy may be obtained upon request from the Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biocompatibility evaluation should follow the methodology of tests for tissue contacting, long-term internal devices.

Toxicological effects (e.g., cytotoxicity, mutagenicity, effects on the immune system, and reproductive and developmental toxicity) should be identified. Complete mutagenicity testing of extracts from the finished, sterilized components of the device should be provided. These tests should include the following: Bacterial mutagenicity, mammalian mutagenicity, deoxyribonucleic acid (DNA) damage, and cell transformation assay.

Acute, subchronic, and chronic toxicity studies using the chemicals recovered by the above exhaustive extraction processes should be provided in the evaluation of the long-term biocompatibility of the device, including dose response and time to response as well as gross and histopathological findings in tissues both surrounding implants and distal to implant sites (lymph nodes, prostate, urethra, bladder, ovaries/testes, liver, kidneys, lungs, uterus, etc.). Animal studies of carcinogenicity, reproductive toxicity, teratogenicity, and later effects on offspring must be performed using scientifically justified test methods. These studies must include animal testing of the extracts from the final sterilized device. Teratology/reproductive testing of the final sterilized device and extractables should be performed in an appropriate species using validated methods. Furthermore, for those devices that

contain silicone gel, a subset of these studies must test the compounds extracted from the materials of the sterilized device for estrogen-like antigonadotropic activity in an appropriate animal model using scientifically valid methods.

Pharmacokinetic/biodegradation studies of all materials contained in the finished device should state all materials of toxicological concern, such as amine, silicone, and fluorosilicone compounds. Of special concern are questions regarding the ultimate fate, quantities, sites/organs of deposition, routes of excretion, and potential clinical significance of silicone shedding, retention, and migration. Data on the distribution and metabolic fate of amine containing components, silicone, and any other materials used in the manufacturing of the device should be supplied.

Animal testing should also be conducted to study the effect of implantation upon device function and material integrity. Complete device chemical characterization and mechanical testing should be performed after devices have been implanted in an appropriate animal model for an appropriate length of time. Of special concern is the material integrity of the pad, cuff, reservoir, pump, tubing, joints, etc., which should be functionally tested and investigated using electron microscopy. The results of this testing should be compared to the failure rates noted during in vitro testing and clinical studies in order to demonstrate that the animal model and study duration chosen are appropriate.

For the implanted mechanical/hydraulic urinary continence device designs that contain silicone gel, or employ a silicone gel as a lubricant, the gel bleed performance of the device, as determined from the results of measurements using a standard diffusion cell maintained at a temperature simulating physiologic conditions using stirred, physiologic saline as a receptacle medium for the bleed, must be reported. Each variation in thickness or device design must be measured to accurately determine diffusion coefficients (with appropriate time dependencies). The chemical identification of the bleed product, including, but not limited to, amine containing components, volatile and nonvolatile silicone cyclics and oligomers below a molecular weight of 1,500 and molecular weight distribution, must be reported.

For the polyurethane covered designs (foam or elastomer), FDA believes that in vivo implant studies must be performed to identify and determine the

bioabsorption, distribution, and elimination of the polyurethane covering (as well as their degradation products) in experimental animals. It is also important to identify and determine the mechanism and rate of degradation, as well as the quantity of TDA or other products generated by the breakdown of polyurethane covered implanted mechanical/hydraulic urinary continence devices after prolonged exposure under physical conditions in animals. Additionally, the agency recommends that retrospective epidemiological and prospective clinical studies be designed to assess the potential of cancer and other long-term complications related to implanted mechanical/hydraulic urinary continence devices containing polyurethane. The agency suggests that these preclinical and epidemiological studies be conducted as a separate subset of implanted mechanical/hydraulic urinary continence device safety studies.

In vitro testing should be conducted at the component, subassembly, and final device levels and must examine all aspects of device design, construction, and operation. This testing should also demonstrate how the device design and manufacturing processes address the failure mode and effects analysis. The failure mode effects analysis should be provided. Copies of the original data sheets from all tests must be included in the PMA. All device failures must be completely described, and the corrective actions taken to eliminate or minimize further recurrence should also be identified.

An adequate number of samples of each model, based on relevant power calculations, will be required. If marketing approval is sought for multiple device versions, each version requires its own set of preclinical tests and results. If sample devices of each available size are not tested, it must be clearly indicated which device sizes were used for each test. The absence of testing on each size must be justified by analysis demonstrating that the results from the tested devices will accurately predict results for the untested device sizes.

The test conditions and acceptance criteria for all tests should be completely explained and justified. All tests should be performed on final, sterilized devices in an environment simulating the possible range of anticipated in vivo conditions (temperatures, pressures, forces, stresses, etc.), where possible. All methods used to determine the condition of the device after testing, e.g., visual examination, electrical

continuity, electron microscope examination, functional testing, etc., must be discussed and justified.

All data collected from in vitro and animal testing, regarding the useful lifetime or long-term reliability of the device, must be compared to data from clinical studies (prospective and/or retrospective) where the useful lifetime of the device has been determined. This comparison must validate the ability of the in vitro and animal tests to accurately predict the useful lifetime of the implanted device.

If accelerated aging is used to demonstrate device durability and reliability, all processes used should be completely described, and the calculations validating the expected aging should be provided.

All physical, chemical, and functional properties of the device should be completely characterized, and the design specifications must be adequately justified. Chemical characterization should include, where applicable, molecular weight and molecular weight distribution, cross-link density, infrared analysis (free isocyanate content, side reaction products), and differential scanning calorimetry. The physical tests should include, but are not necessarily limited to the tests discussed below.

Testing should include the following specific methods or their equivalents:

(1) American Society for Testing Materials (ASTM) Test Method D412 to measure tensile strength, force to breakage, ultimate elongation, and total energy to rupture of the pad, cuff, pump, reservoir, tubing, and bulk of all elastomeric components (with and without incorporated fold flaws) of the finished, sterilized device; dynamic mechanical analysis and fatigue characterization of all elastomeric components particularly those comprising the cuff of the finished, sterilized device; (2) ASTM Test Method D624 to determine tear and abrasion resistance of all components; an applied force at the rate of 1 Hertz versus number of cycles to failure (AF/N) curve (including the minimum force required to rupture the component under a single stroke of applied load), constructed on the basis of cyclical compression testing of intact sterilized devices; and (3) ASTM Test Method F703 (section 7.2) to determine the force to break of adhered or fused joints. A complete report of the cohesivity and penetration testing of the gel must also be reported for the devices containing silicone gel. The results of each of these tests must be compared to the energy, forces, etc., that the device will encounter in vivo.

Life testing should demonstrate the device is sufficiently durable to withstand the demands of use while maintaining operational characteristics sufficient for urethral compression throughout the expected operational lifetime of the implanted mechanical/hydraulic urinary continence device, as stated in the physician and patient labeling. Life testing should include measurements of all component and material wear and bond strengths after the device is cycled between inflated and deflated conditions. A discussion comparing the rate of cycling performed in each test to the approximate maximum rate of cycling of the device in vivo and to the expected longevity of the implant should be included.

Appropriate "downtimes" at predetermined cyclical intervals should be included in the life tests to evaluate relevant performance characteristics and conformance to design specifications. Material characteristics indicative of material degradation that could induce device malfunction should be completely evaluated. Cyclical testing beyond the expected longevity of the implant and recording of failure mode must also be included as part of the life tests.

Filling agent permeability from the reservoir and body of the device must be evaluated to demonstrate that fluid loss due to osmosis will be acceptable over the expected life of the implanted mechanical/hydraulic urinary continence device.

Component-specific tests are also necessary. Reliability over the expected life of the device, proper operation, and conformance to predetermined operational specifications must be demonstrated for each component. Resistance of each component to abrasion, tear, crazing, fracture, material fatigue (including wear between each component), change of position (e.g., valve seats), and permanent deformation also must be demonstrated.

Pad characterization and testing should include, but not be limited to: Measurement of stiffness and rigidity, including resistance to buckling; uniformity of dimensions (if the device is inflated); and wear characteristics.

Cuff characterization and testing should include, but not be limited to: Maximum pressure and expansion capability; measurement of stiffness, including resistance to buckling; resistance to aneurysms; ability of cuff closure to remain inflated under maximum loads expected in vivo; uniformity of inflated dimensions; inflation and deflation characteristics; and wear characteristics at folds in the cuff.

Pump characterization and testing should include, but not be limited to: The range of volumes displaced per stroke; minimum force required to affect fluid displacement; squeeze force versus fluid displacement; inflation effort, defined as pump force times the number of strokes required for full device activation; and ability of the implanted mechanical/hydraulic urinary continence device to maintain its set pressure after repeated punctures to its pressure adjustment port with both new devices and devices evaluated in the reliability tests.

Valve characterization and testing should include, but not be limited to: Pump output pressure required to affect valve opening for device activation; tactile pressure/force required to affect valve opening, against fully inflated cuffs, for deflation; back pressure required for valve failure; maximum pressure differential across closed valve at full inflation and deflation, and the leakage rates at these pressures; prevention of spontaneous deflation under movements and loads simulating those expected to be sustained by the implanted device in an inflated state; and potential for valve failure which could result in an inability to inflate or deflate the cuff.

Reservoir characteristics should be evaluated and should include, but not be limited to: Volume capacity; pressures generated over the inflation/deflation cycle; rate of maximum fluid outflow and inflow; wear characteristics if a fold in the reservoir envelope occurs; and durability tests demonstrating adequate resistance to fatigue caused by cyclic external compression applied radially to inflated reservoir.

Tubing testing should include, but not be limited to: Tensile characteristics (with and without tubing connectors, if any); tear or rupture resistance; kink resistance; wear characteristics if a fold in the tubing develops; and ability of the tubing to remain intact under loads simulating and exceeding those expected in vivo.

Testing to demonstrate the inflation/deflation characteristics of the device should include, but not be limited to: Amount of pressure generated during inflation of the cuff; amount of pressure drop (deflation) and rise (inflation) per unit time; ability to maintain the inflated cuff dimensions; and time to fully inflate and deflate the cuff from specified starting pressures.

All bonds within the device and between components should undergo appropriate testing including, but not be limited to measurement of bond shear and tensile strength. Bond strength

should exceed the loads expected during device handling and after implantation.

Other components of the implanted mechanical/hydraulic urinary continence device or accessories, such as tubing connectors, extension adapters, and specialized tools used during the insertion procedure, should be evaluated appropriately. Testing of these components or accessories should reflect the anticipated conditions of use; for example, tubing connectors should be demonstrated to be able to maintain connection to the device for the expected life of the device.

C. Clinical Data

Valid scientific evidence, as defined in § 860.7(c)(2), which includes information from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there are reasonable assurances of the safety and effectiveness of the implanted mechanical/hydraulic urinary continence device. Detailed protocols for the clinical trials, with explicit patient inclusion/exclusion criteria and well-defined followup schedules, should be specified. FDA believes that 5-year followup data are necessary in order to characterize the safety and effectiveness of the device over its expected lifetime; however, appropriately justified alternate followup schedules will be considered. Any deviations from the protocol should be stated and justified. Time-course presentations of restoration of continence (dryness) or significant improvement in continence, as well as other information on the anatomical and physiological effects of the implanted mechanical/hydraulic urinary continence device (including all adverse events) should be provided. Full patient accounting should be reported, including: (1) Theoretical followup (the number of patients that would have been examined if all patients were examined according to their followup schedules); (2) patients lost to followup, excluding deaths, should include measures taken to minimize such events (with all available information obtained on patients lost to followup) and should not exceed 20 percent over the course of the study; (3) time course of revisions, including all explant and repair data; and (4) time-course of deaths (stating the cause of death, including the reports

from any postmortem examinations). As part of this patient accounting, each clinical report should clearly state the date that the data base was closed to the addition of new information. Detailed patient demographic analyses and characterizations should be presented to show that the patients enrolled in the study are representative of the population for whom the device is intended.

A statistical demonstration, based on the number of patients who complete the required study period, should show that the sample size of the clinical study is adequate to provide accurate measures of the safety and effectiveness of this device. The statistical demonstration should identify the effect criteria, clinically reasonable levels for Type I (alpha) and Type II (beta) errors, and anticipated variances of the response variables. The statistical demonstration should also provide any assumptions made and all statistical formulas used (with copies of any references). A complete description of all patient randomization techniques used, and how these techniques were employed to exclude potential sources of bias, should be provided. Statistical justifications for pooling across several demographic or surgical variables, such as the etiology and duration of incontinence, age, gender, concomitant medical conditions, various anatomical abnormalities, the type or model of the device implanted, the number and type of treatments (if any) attempted to restore continence prior to device implantation, device usage (initial implantation versus revision), investigational site, degree of patient motivation and manual dexterity, surgeon experience and technique, and pad or cuff placement site, should be provided. The data collected and reported should include all necessary variables in order to permit stratification and analysis of the study data required to evaluate the risk/benefit ratio for each clinically relevant subpopulation of patients.

Appropriate concurrent control/comparison groups should be included and justified and, if not, their absence must be justified. All hypotheses to be tested must be clearly stated. Appropriate statistical techniques must be employed to test these hypotheses as support for claims of safety and effectiveness. For each relevant subgroup, a sufficient number of patients need to be followed for a sufficient length of time to support all claims (explicit and implied) in any PMA submission.

To evaluate the risks to the patient from the implanted mechanical/

hydraulic urinary continence device, clinical studies should include time-course presentations of clinical data demonstrating the presence or absence of tissue erosion, infection, pain/discomfort, injury to the upper urinary tract due to either urinary retention or hydronephrosis, continued or worsened incontinence, leakage, wear, tubing kinking/breaking or disconnection, pump failure, cuff or pad failure, hematoma, seroma, inguinal hernia formation, fibrous capsule formation, fistula formation from urethral erosion, urethral scarring, bleeding, urethral stricture, development of bladder hyperreflexia, reoperation, wound dehiscence, pelvic abscess, and fistula to the skin, including any effects on the immune system (both local to the device and systemic) and the reproductive system, without regard to the device relatedness of the event. The diagnostic criteria for each type of immunological and allergic phenomenon should be defined at the beginning of the study, and all cases should be well-documented utilizing these criteria. Patients must be regularly monitored for the occurrence of such adverse events for a minimum of 5 years post-implantation, or until physical maturity of the subject (whichever occurs later).

The effectiveness of the device may be assessed by an objective and standardized recording/measurement of: (1) The ability of the device in vivo to either restore or significantly improve urinary continence; and (2) the enhancement of a patient's quality of life following implantation of the device; both of which should be balanced against any risk of illness or injury from use of the device. FDA understands that evaluation of the degree of benefit involves, in part, an assessment of patient quality of life, which relates to the postoperative function of the device. Such evaluation includes subjective factors and relates to patient expectations. Assessments of the in vivo performance of the device's function, on the other hand, should provide some objective measure of device effectiveness.

Documentation of the anatomical and physiologic outcomes of implantation of an implanted mechanical/hydraulic urinary continence device shall include:

(1) Regular postsurgical evaluations of the functional (i.e., inflation and deflation) characteristics of the device for at least 5 years postimplantation, or until physical maturity of the subject (whichever occurs later);

(2) Periodic postsurgical urodynamic testing (such as measurements of leak point pressure and the volume of urine leaked into a pad after a standard set of

maneuvers) during this followup period, with comparisons to baseline measurements;

(3) Regular postsurgical assessments of incontinence grade (possibly obtained from patient voiding diaries or the number of pads required per day to keep dry), as compared to baseline values; and

(4) Patient assessments of the mechanical function of the implant (such as ease of activation) during this followup period (which may be influenced by the manual dexterity or motivation of the patient).

Documentation of the effect of the device upon the patient's quality of life shall include:

(1) Prospective research designs, including pre- and postsurgical repeated measures for at least 5 years postimplantation, or until physical maturity of the subject (whichever occurs later);

(2) Standardized test questions rather than informal, yet-validated questionnaires; and

(3) Comparisons of the postsurgical scores to those measured prior to device implantation.

Any PMA for the implanted mechanical/hydraulic urinary continence device should separately analyze the degree of device safety and effectiveness by the following variables: (1) Etiology; (2) duration and degree of urinary incontinence; (3) the device type or model implanted; (4) gender; and (5) age. Furthermore, for each explantation procedure performed on the study subjects, the following information must be provided: (1) The mode of failure of the removed device; (2) whether or not the explanted device was replaced with a new device; and (3) either the manufacturer, type and model of the new device implanted (if another implanted mechanical/hydraulic urinary continence device was implanted), or the type of treatment (if any) that the patient received for his/her incontinence (if revision surgery was not performed). Additionally, the effect of the presence of these implants upon future medical diagnoses/treatments involving the lower pelvic region in recipients of implanted mechanical/hydraulic urinary continence devices must be analyzed. Furthermore, any accessories sold with the implanted mechanical/hydraulic urinary continence device must be shown to have been effectively used in implant procedures without adverse effects. Finally, each clinical investigation should validate the physician and patient instructions for use (labeling) that were used, particularly the instructions regarding the selection of

the appropriate device size (if applicable).

For polyurethane foam covered implants, the following additional information needs to be presented:

(1) The kinetics of end products generated from the degradation of the polyurethane material (in vivo);

(2) The frequency and incidence of infection and complication of retrieval of the implant by surgeons; and

(3) The neoplasticity of these materials and products, as well as their general toxicity, including neurological, physiological, biochemical, and hematological effects, as well as pathology following prolonged and repeated exposure to polyurethane foam covered implanted mechanical/hydraulic urinary continence devices.

Any epidemiological studies submitted should contain sufficient subjects to permit detection of a small, but clinically significant, increase in one or more connective tissue diseases (especially scleroderma) that may be associated with the use of the device.

The agency believes that insufficient time has elapsed to permit a direct evaluation of the risks of cancer and immune related connective tissue disorders posed by the presence of silicone in the human body, and that insufficient epidemiological and experimental animal data are available to make a reasonable and fair judgment of these risks. Furthermore, the potential long-term risk of hydronephrosis and/or decreases in renal function in patients implanted with the implanted mechanical/hydraulic urinary continence device, due to the chronic elevation of urethral resistance experienced postimplantation, has yet to be quantified and is a concern of the agency. Therefore, the agency will require long-term postapproval followup for any implanted mechanical/hydraulic urinary continence device permitted in commercial distribution. Well-designed clinical prospective studies with long-term followup together with experimental animal studies will be considered essential to the determination of the safety and effectiveness of the device. Further, these clinical studies must collect long-term data on the reproductive/teratogenic effects of the device as well as on the later effects on the offspring.

The risk/benefit assessment (as with the entire PMA) must rely on valid scientific evidence as defined in § 860.7(c)(2) from well-controlled studies as described in § 860.7(f) in order to provide reasonable assurance of the safety and effectiveness of the implanted mechanical/hydraulic

continence device in the treatment of urinary incontinence.

D. Labeling

Copies of all proposed labeling for the device including any information, literature, or advertising that constitutes labeling under section 201(m) of the act (21 U.S.C. 321(m)), should be provided. The general labeling requirements for medical devices are contained in 21 CFR part 801. These regulations specify the minimum requirements for all devices. Additional guidance regarding device labeling can be obtained from FDA's publication "Labeling: Regulatory Requirements for Medical Devices," and from the Office of Device Evaluation's "Device Labeling Guidance"; both documents are available upon request from the Division of Small Manufacturers Assistance (address above). Highlighted below is additional guidance for some of the specific labeling requirements for implanted mechanical/hydraulic urinary continence devices.

The intended use statement should include the specific indications for use and identification of the target populations. Specific indications and target populations must be completely supported by the clinical data described above. For example, it may be necessary to restrict the intended use to patients who have failed prior less invasive therapies and/or to patients with specific etiologies of incontinence in whom safety and effectiveness have been demonstrated.

The directions for use should contain comprehensive instructions regarding the preoperative, perioperative, and postoperative procedures to be followed. This information includes, but is not necessarily limited to: (1) A description of any preimplant training necessary for the surgical team; (2) a description of how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies must be on hand), and implanted mechanical/hydraulic urinary continence device (e.g., handling instructions, resterilization instructions) for device implantation; (3) instructions for implantation, including possible surgical approaches, sizing, fluid adjustment (including what filling solutions may be used and how they must be prepared), device handling, and intraoperative test procedures to ensure implant functionality and proper placement; and (4) instructions for followup, including whether antibiotic prophylaxis is recommended during the postimplant period and/or during any subsequent dental or other surgical procedures, how to determine when

patients are ready to activate the device, and how to evaluate, and how often to evaluate, proper functionality and placement. The directions should instruct caregivers to specifically question patients prior to surgery for any history of allergic reaction to any of the device materials or filling agents. Troubleshooting procedures should be completely described. The directions for use should incorporate the clinical experience with the implant, and should be consistent with those provided in other company-provided labeling.

The labeling should include both implant and explant forms to allow the sponsor to adequately monitor device experience. The explant form should allow collection of all relevant data, including the reason for the explant, any complications experienced and their resolution, and any action planned (e.g., replacement with another implant).

Patient labeling must be provided which includes the information needed to give prospective patients realistic expectations of the benefits and risks of device implantation. Such information should be written and formatted so as to be easily read and understood by most patients and should be provided to patients prior to scheduling implantation, so that each patient has sufficient time to review the information and discuss it with his or her physician(s). Technical terms should be kept to a minimum and should be defined if they must be used. Patient information labeling should not exceed the seventh grade reading comprehension level.

The patient labeling should provide the patient with the following information: (1) The indications for use and relevant contraindications, warnings, precautions and adverse effects/ complications should be described using terminology well known and understood by the average layman; (2) the anticipated benefits and risks associated with the device must be provided to give patients realistic expectations of device performance and potential complications. The known, suspected and potential risks of device implantation should be identified and the consequences, including possible methods of resolution, should be described; (3) alternatives available to the use of the device, including less invasive treatments, should be identified, along with a description of the associated benefits and risks of each. The patient should be advised to contact his physician for more information on which of these alternatives might be appropriate given his specific condition; (4) instructions for how to use the

device must be provided to the patient. This information should include the expected length of recovery from surgery and when to attempt activation following implantation, whether and how often the device should be periodically cycled (if applicable), warnings against certain actions that could damage the device, how to identify conditions that require physician intervention, who to contact if questions arise, and other relevant information; (5) the fact that the implant should not be considered a "lifetime" implant must be emphasized. Where possible, the patient labeling should provide information on the approximate number of revisions necessary for the average patient, and indicate the average longevity of each implant so patients are fully aware that additional surgery for device modification, replacement, or removal may be necessary. This information must be supported by the clinical experience (i.e., not merely bench studies) with the implant or by published reports of experience with similar devices.

The physician's labeling should instruct the urologist or implanting surgeon to provide the implant candidate with the patient labeling prior to surgery to allow each patient sufficient time to review and discuss this information with his physician(s).

The adequacy and appropriateness of the instructions for use provided to physicians and patients should be verified as part of the clinical investigations.

Applicants should submit any PMA in accordance with FDA's "Premarket Approval (PMA) Manual." The manual is available upon request from the Division of Small Manufacturers Assistance (address above).

III. Comments

Interested persons may, on or before June 15, 1995, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Those wishing to make comments are encouraged to discuss all aspects of the proposed findings regarding the following topics:

(1) Degree of risk, illness, or injury associated with the use of the implanted

mechanical/hydraulic urinary continence device;

(2) Laboratory, animal, and human studies required in a PMA for the device in order to assess its safety and effectiveness;

(3) Feasibility of these studies within the time permitted by the act, etc.; and

(4) Benefits to the public from the use of the device.

The comments must discuss in detail, for example, the reasons why important new information on the safety and effectiveness of the device could not feasibly be submitted within the time permitted, or why animal studies may not be available to assess long-term effects such as connective tissue disorders, or that carefully designed epidemiological studies may not be available to evaluate the long-term silicone related illnesses, etc.

The Center for Devices and Radiological Health staff are available to provide guidance to manufacturers on any proposed laboratory, animal, or epidemiological studies needed in a PMA.

IV. Opportunity to Request a Change in Classification

Before requiring the filing of a PMA or a notice of completion of a PDP for a device, FDA is required by section 515(b)(2)(A)(i) through (b)(2)(A)(iv) of the act and 21 CFR 860.132 to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to its classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the act.

A request for a change in the classification of the implanted mechanical/hydraulic urinary continence device is to be in the form of a reclassification petition containing the information required by § 860.123 (21 CFR 860.123), including new information relevant to the classification of the device, and shall, under section 515(b)(2)(B) of the act, be submitted by March 2, 1995.

The agency advises that to assure timely filing of any such petition, any request should be submitted to the Dockets Management Branch (address above) and not to the address provided in § 860.123(b)(1). If a timely request for a change in the classification of the implanted mechanical/hydraulic urinary continence device is submitted, the agency will, by April 17, 1995, after consultation with the appropriate FDA advisory committee and by an order published in the **Federal Register**, either deny the request or give notice of its intent to initiate a change in the

classification of the device in accordance with section 513(e) of the act and 21 CFR 860.130.

V. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866

directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because PMA's for this device could have been required by FDA as early as June 30, 1986, and because firms that distributed this device prior to May 28, 1976, or whose device has been found by FDA to be substantially equivalent will be permitted to continue marketing the implanted mechanical/hydraulic urinary continence device during FDA's review of the PMA or notice of completion of the PDP, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

List of Subjects in 21 CFR Part 876

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 876 be amended as follows:

PART 876—GASTROENTEROLOGY-UROLOGY DEVICES

1. The authority citation for 21 CFR part 876 continues to read as follows:

Authority: Secs. 501, 510, 513, 515, 520, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 360, 360c, 360e, 360j, 371).

2. Section 876.5280 is amended by revising paragraph (c) to read as follows:

§ 876.5280 Implanted mechanical/hydraulic urinary continence device.

* * * * *

(c) *Date PMA or notice of completion of a PDP is required.* A PMA or notice of completion of a PDP is required to be filed with the FDA on or before (insert date 90 days after the effective date of a final rule based on this proposed rule), for any implanted mechanical/hydraulic

urinary continence device that was in commercial distribution before May 28, 1976, or that has on or before (insert date 90 days after the effective date of a final rule based on this proposed rule), been found to be substantially equivalent to the implanted mechanical/hydraulic urinary continence device that was in commercial distribution before May 28, 1976. Any other implanted mechanical/hydraulic urinary continence device shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: January 10, 1995.

D.B. Burlington,

Director, Center for Devices and Radiological Health.

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DEPARTMENT OF COMMERCE

Patent and Trademark Office

37 CFR Parts 1 and 3

[Docket No. 941120-4320]

RIN 0651-AA76

Changes to Implement 20-Year Patent Term and Provisional Applications

AGENCY: Patent and Trademark Office, Commerce.

ACTION: Proposed rule; change in public hearing location.

SUMMARY: The public hearing scheduled for February 16, 1995, concerning the notice of proposed rulemaking published on December 12, 1994 at 59 FR 63951, with a supplemental request for comments published on January 17, 1995, at 60 FR 3398, will be held in the Roanoke Room, Stouffer Hotel at Crystal City, 2399 Jefferson Davis Highway, Arlington, Virginia, instead of in the Commissioner's Conference Room, Crystal Park 2, Room 912, 2121 Crystal Drive, Arlington, Virginia, as previously indicated. The change in location is being made to accommodate more people.

DATES: Written comments must be submitted on or before February 17, 1995. A public hearing will be held Thursday, February 16, 1995, at 9:30 a.m., in the Roanoke Room, Stouffer Hotel at Crystal City, 2399 Jefferson Davis Highway, Arlington, Virginia. Oral testimony on the effects of patent expiration dates and patent term extension will begin at 1:00 p.m. Requests to present oral testimony should be received on or before February 14, 1995.