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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 876

[Docket No. 92N-0445]

Gastroenterology-Urology Devices; Effective Date of Requirement for Premarket Approval of the Penile Inflatable Implant

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to require the filing of a premarket approval application (PMA) or a notice of completion of a product development protocol (PDP) for the penile inflatable implant, a generic type of medical device intended for the treatment of erectile dysfunction. This regulation reflects FDA's exercise of its discretion to require PMA's or PDP's for preamendments devices and is consistent with FDA's stated priorities and Congress' requirement that class III devices are to be regulated by FDA's premarket review. This action is being taken under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the amendments), the Safe Medical Devices Act of 1990, and the Food and Drug Administration Modernization Act of 1997.

DATES: This rule is effective [*insert date of publication in the Federal Register*].

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

SUPPLEMENTARY INFORMATION:**I. Introduction**

In the **Federal Register** of November 23, 1983 (48 FR 53023), FDA published a final rule classifying into class III (premarket approval) the penile inflatable implant, a medical device. Section 876.3350 (21 CFR 876.3350) of FDA's regulations setting forth the classification of the penile inflatable implant applies to: (1) Any penile inflatable implant that was in commercial distribution before May 28, 1976, and (2) any device that FDA has found to be substantially equivalent to a penile inflatable implant in commercial distribution before May 28, 1976.

In the **Federal Register** of April 28, 1993 (58 FR 25902), FDA published a proposed rule, under section 515(b) of the act (21 U.S.C. 360e(b)), to require the filing of PMA's or PDP's for the classified penile inflatable implant and all substantially equivalent devices (hereinafter referred to as the April 1993 proposed rule). In accordance with section 515(b)(2)(A) of the act, FDA included in the preamble, the agency's proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the premarket approval requirements of the act, and (2) the benefits to the public from use of the device.

The preamble also provided an opportunity for interested persons to submit comments on the proposed rule and the agency's proposed findings. Under section 515(b)(2)(B) of the act, it also provided an opportunity for interested persons to request a change in the classification of the device based on new information relevant to its classification. Any petition requesting a change in the classification of the penile inflatable implant was required to be submitted by May 13, 1993. The comment period initially closed on June 28, 1993. In the **Federal Register** of July 1, 1993 (58 FR 35416), FDA extended the comment period for 60 days to August 27, 1993, to ensure that there was adequate time for preparation and submission of comments on the proposed rule.

The agency received 32 comments in response to the April 1993 proposed rule. These comments were from physicians and other health care providers, professional organizations, physician groups, manufacturers, and consumers and other individuals. Most of the comments supported the proposed rule.

This regulation is final upon publication and requires PMA's or notices of completion of a PDP for all penile inflatable implants classified under § 876.3350 and all devices that are substantially equivalent to them. PMA's or notices of completion of a PDP for these devices must be filed with FDA within 90 days of the effective date of this regulation. (See section 501(f)(1)(A) of the act (21 U.S.C. 351(f)(1)(A)).) This regulation does not include the penile rigidity implant (21 CFR 876.3630).

II. Summary and Analysis of Comments and FDA's Response

A. General Comments

(Comment 1) FDA received 23 comments from individual physicians and 2 comments from professional medical organizations. Although the majority of these comments did not object to the proposed call for PMA's or PDP's, they voiced the following common concerns: (1) Erectile dysfunction is a serious medical problem affecting tens of millions of American men and their partners, (2) removal of this device from the U.S. market would be detrimental to public health, and (3) citing the 25 years of use of the device, sufficient historical data exist to evaluate the safety and effectiveness of the penile inflatable implant. This last concern was also noted in two comments from penile inflatable implant manufacturers, which stated that the decades of medical literature regarding the risks and benefits of this device provide sufficient evidence of its safety and effectiveness. Several comments remarked that FDA has overstated the risks of the inflatable penile implant.

FDA agrees that erectile dysfunction is a significant medical problem that negatively affects the lives of more than 10 million men in the United States. Furthermore, since penile inflatable

implants represent an important option in the treatment of erectile dysfunction, FDA agrees with these comments that removal of the penile inflatable implant from the market would negatively impact public health. As a result of this concern, FDA has taken the following steps to promote the continued availability of the penile inflatable implant during the call for PMA's or PDP's:

- (1) FDA issued the guidance document entitled "Draft Guidance for Preparation of PMA Applications for Penile Inflatable Implants" in March 1993 (the 1993 guidance document) to provide industry with detailed recommendations on the content of PMA's;
- (2) FDA has communicated closely with each penile inflatable implant manufacturer to address the concerns identified in the proposed rule using least burdensome methods, as well as provided recommendations on the design of preclinical and clinical studies; and
- (3) FDA intentionally postponed the call for PMA's or PDP's to allow manufacturers to collect sufficient data to support the filing of a PMA or PDP.

FDA agrees with the comments that there is a significant amount of information in the published and unpublished literature regarding the penile inflatable implant. However, to FDA's knowledge, these studies are neither sufficiently detailed nor properly designed to perform a statistically valid evaluation of the safety and effectiveness of any of the specific device models currently on the market. As recommended in the 1993 guidance document, PMA's or PDP's should contain safety and effectiveness information on the specific device model(s) proposed in the application. Although a large body of historical data exists regarding the clinical outcomes of models of penile inflatable implants that are no longer marketed, there is less information available regarding the safety and effectiveness of currently-marketed models. However, if sufficient historical information exists to document the safety and effectiveness of a particular penile inflatable implant model that a manufacturer desires to market, or if data about earlier models are directly relevant to a particular device, FDA encourages the use of these data in support of a PMA or PDP for that model.

While FDA agrees that the April 1993 proposed rule may have overstated the risks of some of the specific penile inflatable implant models that are currently on the market, we believe that the information in the proposed rule represents a reasonable estimate of the risks and benefits of the entire category of penile inflatable implants. As noted in many of these comments, manufacturers have made numerous design modifications to improve the reliability of the penile inflatable implant and the medical community continues to improve the patient selection criteria, patient counseling information, operative technique, and postoperative care to reduce the incidence of complications. Therefore, FDA expects the rates of complications reported in PMA's or PDP's for particular penile inflatable implants to be lower than estimated from a review of the literature on the entire device category. However, in writing the proposed call for PMA's or PDP's, FDA must consider the risks and benefits of all penile inflatable implants that currently have legally marketed status in the United States.

(Comment 2) FDA received one comment from a penile inflatable implant recipient, who is supportive of the proposed call for PMA's or PDP's. This consumer has received a total of four devices to date, and his most recent device has failed, requiring replacement. He states that the penile inflatable implant affects both his quality of life and manhood.

FDA agrees that the potential benefits of a penile inflatable implant include improvements in quality of life and self-image, and notes that these secondary benefits of penile inflatable implant implantation were cited in the proposed call for PMA's or PDP's. Furthermore, FDA believes that requiring the submission of PMA's or PDP's for the penile inflatable implant will allow FDA to assess the risks and benefits of specific devices in order to determine whether there is reasonable assurance of their safety and effectiveness.

(Comment 3) One comment stated that FDA's assessment of the risks of penile inflatable implants is inconsistent with FDA's assessment of the risks of class II silicone prostheses such as the bone cap (21 CFR 888.3000), chin prosthesis (21 CFR 878.3550), the ear prosthesis (21 CFR 878.3590), and the finger joint prosthesis (21 CFR 888.3230).

FDA is aware of the existence of information on silicone and silicone-containing prostheses, and expects that applicants may include such information in their submissions to support the safety and effectiveness of the penile inflatable implant. However, FDA does not believe that the existing information on silicone and silicone-containing prostheses can be used as the sole basis of establishing the safety and effectiveness of the penile inflatable implant, and believes that a determination of safety and effectiveness of the penile inflatable implant must be made, at least in part, on data collected on each particular device for which a PMA or PDP is submitted. FDA will consider all information contained in PMA's and PDP's in determining whether there is reasonable assurance of safety and effectiveness of this device.

(Comment 4) Many comments noted that FDA was incorrect in stating that some penile inflatable implant models contain silicone gel. These comments concluded, therefore, that the risks of silicone gel do not apply to the penile inflatable implant.

FDA disagrees with the comments that no penile inflatable implant contains silicone gel. Although silicone gel has never been used as a penile inflatable implant inflation medium, FDA is aware of at least one device model, no longer marketed in the United States, that contained silicone gel within its cylinder tip. FDA agrees with the comments that the potential risks of silicone gel are not applicable to penile inflatable implants that do not contain silicone gel.

The agency would not expect PMA's or PDP's for those devices to address the risks related to silicone gel.

(Comment 5) One comment objected that Congress never intended "old" preamendments medical devices to undergo the same scrutiny as "new" postamendments medical devices.

FDA does not believe that Congress intended to differentiate between "old" preamendments devices and "new" postamendments device with respect to the requirement that valid scientific evidence is needed to support PMA approval. Neither section 513(a)(3) (21 U.S.C. 360c(a)(3)) nor section 515(d) of the act makes any distinction between "old" and "new" devices with regard to any aspect of the requirement for PMA approval.

(Comment 6) One comment stated that FDA should allow an appropriate timeframe prior to issuance of the call for PMA's or PDP's for the following reasons: (1) FDA needs sufficient time to develop additional guidance on the data requirements for PMA's and PDP's; (2) since several of the main suppliers of silicone and polyurethane raw materials have announced a planned withdrawal of these products from the market, penile inflatable implant manufacturers need sufficient time to qualify and test new materials; and (3) device manufacturers need sufficient time to collect the preclinical and clinical data recommended by FDA.

FDA believes there has been sufficient time for PMA and PDP sponsors to develop data and address the issues identified as potential risks. Section 515(b) of the act does not require the agency to provide guidance on the contents of specific PMA's. However, FDA issued the 1993 guidance document to provide industry with detailed recommendations on the appropriate data to be included in PMA's and PDP's for penile inflatable implants. The 1993 guidance document is available from the Internet at www.fda.gov/cdrh/ode/oderp810.html. In order to receive the 1993 guidance document via your fax machine, call the CDRH Facts-On-Demand (FOD) system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system and then enter the document number (810) followed by the pound sign (#). Follow the remaining voice prompts to complete your request. While the 1993 guidance document continues to remain in effect, FDA plans to revise this document in the near future to incorporate many of the comments subsequently received from the industry and public. Furthermore, the agency encourages penile inflatable implant manufacturers to meet with FDA before submitting a PMA or PDP to obtain additional guidance regarding the recommended data to submit to demonstrate the safety and effectiveness of each specific device model proposed for market approval.

In addition, the period of time between the classification of the device in 1983 and the date by which PMA's must be filed is more than 16 years. Thus, FDA believes that sufficient time and guidance have been provided to allow sponsors to develop the data for a PMA submission.

FDA agrees that dialogue with industry and with the scientific community and medical community is important. To elicit early public discussion on the 1993 guidance document and the agency's plans to call for PMA's or PDP's for the penile inflatable implant, FDA called a meeting of the Gastroenterology and Urology Devices Advisory Panel on April 15, 1993, to discuss these topics. Following publication of the proposed call for PMA's or PDP's, FDA communicated closely with each penile inflatable implant manufacturer to address the concerns identified by FDA in the April 1993 proposed rule, as well as provide recommendations on the design of preclinical and clinical studies for their particular device models. Furthermore, FDA staff have been and continue to be accessible to discuss PMA and PDP content information with industry and the scientific and medical community.

(Comment 7) One comment stated that FDA was incorrect in its determination that the penile inflatable implant has a high priority for initiating a proceeding to require premarket approval due to inappropriate comparison to potential adverse effects of silicone gel breast implants and due to the volume of Medical Device Reports (MDR's) received to date for penile inflatable implants. The comment further noted that an early call for PMA's or PDP's is unwarranted since the penile inflatable implant was not included in the January 6, 1989 (54 FR 550), list of 31 "high priority" preamendments class III devices.

FDA believes the call for PMA's or PDP's for this device cannot be considered an "early" call in light of its classification in 1983 and the proposed call for PMA's in 1993.

By adding section 515(i) to the act in the Safe Medical Devices Act of 1990 (Public Law 101-629), Congress made it clear that it expected FDA to move forward expeditiously to either require premarket approval or notices of completion of PDP for all preamendments class III devices or to reclassify them into class I or class II. Therefore, FDA believes that it is appropriate to issue this final rule at this time.

B. Infection

(Comment 8) There were 19 comments on the risk of infection. Several comments stated that the incidence of infection associated with the implantation of penile inflatable implants is not any higher than it is for other implantation surgeries. Many of these comments further stated that the risk of infection is minimized by proper patient selection, meticulous attention to sterile technique during device implantation, and adherence to appropriate postoperative precautions. Several comments stated that infection, if it occurs, often can be successfully controlled without the need for device removal if it is recognized early and treated with appropriate aggressive antibiotic therapy with or without drainage and wound irrigation. One comment added that infections of penile inflatable implants only rarely result in an inability to replace the device due to corporeal fibrosis and cavernositis.

FDA agrees that the risk of infection can be minimized by proper patient selection, surgical precautions, and postoperative care. However, FDA believes that it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence and consequences of infection associated with the implantation of the penile inflatable implant. As noted in the 1993 guidance document, FDA is requesting information on the incidence of infection for this device.

C. Migration and Extrusion

(Comment 9) There were 13 comments regarding the risks of migration and extrusion. These comments stated that migration and extrusion of penile inflatable implants occur infrequently, are directly related to infection or excessive pressure of the prosthesis on surrounding tissues, and are minimized by properly placing an appropriately sized device using appropriate surgical techniques. For these reasons, several comments stated that migration and extrusion should not be labeled as "significant risks" of implantation of the device.

While FDA agrees that migration and extrusion can be minimized by proper device sizing and placement, insufficient information is available to determine the frequency of this event or its effects. Therefore, FDA believes that it is important for studies submitted in a PMA or PDP

to provide accurate information on the incidences of migration and extrusion associated with the implantation of the penile inflatable implant.

FDA disagrees with the comment that migration and extrusion are not significant risks. Migration and extrusion of the penile inflatable implant can lead to surgical intervention, making them serious risks to health. As noted in the 1993 guidance document, FDA is requesting information to address the incidences of migration and extrusion for this device.

D. Erosion

(Comment 10) There were 13 comments regarding the risk of erosion. These comments stated that, similar to migration and extrusion, erosion of penile inflatable implants occurs infrequently, is directly related to infection or excessive pressure of the prosthesis on surrounding tissues, and is minimized by properly placing an appropriately sized device using appropriate surgical techniques. For these reasons, several comments stated that erosion should not be labeled as a "significant risk" of implantation of the device.

While FDA agrees that the risk of erosion can be minimized by proper device sizing and placement, insufficient information is available to determine the frequency of this event or its consequences. Therefore, FDA believes that it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence of erosion associated with the implantation of the penile inflatable implant.

FDA disagrees with the comment that erosion is not a significant risk. Erosion of the penile inflatable implant can require surgical intervention, making it a serious risk to health. As noted in the 1993 guidance document, FDA is requesting information to address the incidence of erosion for this device.

E. Fibrous Capsule Formation

(Comment 11) FDA received 15 comments regarding the risk of fibrous capsule formation. Most of these comments stated that fibrous capsule formation is part of the body's normal reaction

to an implanted device, and is not harmful to the patient. One comment stated that fibrous capsule formation does not adversely affect the function of the penile inflatable implant, while several others acknowledged that the fibrotic capsule can keep the reservoir or other device components from completely filling, thus hindering the ability of the device to fully inflate or deflate. Many of the comments regarding the effect of fibrous capsule formation upon inflation and deflation of the penile inflatable implant further stated that this risk can be minimized by leaving the device deflated during the healing period so that the capsule formed around the reservoir minimally impedes refilling. One comment further stated that FDA was wrong to refer to fibrous capsule formation as a "foreign body reaction," since fibrotic reactions are not only related to the material of the implant but also to other factors such as loading forces on the implant and the patient's biological tendency to form a scar. Two comments stated that fibrous capsule formation is only problematic with static prostheses, such as breast implants, and, therefore, is not a concern with penile inflatable implants.

FDA agrees that fibrous capsule formation is part of the body's normal reaction to all implanted devices including penile inflatable implants, and is usually not life-threatening. Also, FDA recognizes that the severity of this risk to health is dependent upon multiple factors other than foreign body reaction. Furthermore, FDA agrees that the risk of inflation/deflation difficulties secondary to fibrous capsule formation around the reservoir can be minimized by proper postoperative care. However, FDA believes that fibrous capsule formation can affect the function of the penile inflatable implant and is potentially serious. Severe fibrous capsule formation has been reported to impede the ability of the penile inflatable implant to operate as it is designed, which reduces or eliminates the benefit of the device. In addition, the recipient may then elect to have his implant surgically explanted and have a second device implanted. This additional surgery makes fibrous capsule formation a potentially serious adverse event. As noted in the 1993 guidance document, FDA is requesting information to address the incidence of fibrous capsule formation for this device.

F. Mechanical Malfunctions

(Comment 12) There were 14 comments regarding the risk of mechanical malfunction. All of these comments stated that while early models of penile inflatable implants were associated with high rates of mechanical malfunction, improvements in device design and implantation technique have steadily decreased the failure rate. Several of these comments added that the mechanical malfunction rate of current device designs ranges from "rare" to 1 to 3 percent. One comment added that FDA's statement that a penile inflatable implant "should not be considered a lifetime implant" is inaccurate, since prostheses may be expected to endure indefinitely with the proviso that there is a risk of mechanical failure.

FDA agrees that the mechanical malfunction rate of the penile inflatable implant has significantly decreased as compared to early models. Despite this observed trend, however, insufficient information is available to determine the frequency of this event for each of the particular device models that manufacturers intend to market following the effective date of this regulation. Therefore, FDA believes that it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence of mechanical malfunction associated with the implantation of the penile inflatable implant.

FDA disagrees with the comment that the penile inflatable implant can be considered a lifetime implant. As complex mechanical devices, penile inflatable implants are subject to wear over time and, therefore, have finite lifetimes. The fact that each device carries the risk of mechanical failure, as acknowledged in the comment, underscores the need to inform patients that the device should not be expected to function indefinitely.

G. Iatrogenic Disorders

(Comment 13) FDA received 11 comments regarding the risk of iatrogenic disorders. These comments stated that iatrogenic disorders occur infrequently, are minimized with proper operative technique and surgeon experience, are not directly related to the device, and are medical issues outside the domains of clinical testing and premarket review.

FDA agrees that iatrogenic disorders are infrequent events which are reduced through adherence to proper surgical technique. FDA also agrees that the medical community has had a major role in defining these surgical practices in an effort to minimize the incidence of iatrogenic disorders. However, FDA believes that iatrogenic disorders are, in part, device related, since issues of sizing, device assembly, and implantation technique are influenced by the specific device design being implanted. As a result, FDA believes that iatrogenic disorders should be evaluated in the clinical testing and premarket review of penile inflatable implants so that the product-specific information obtained from such testing is appropriately incorporated into the labeling of that device model. As noted in the 1993 guidance document, FDA is requesting information to address the incidence of iatrogenic disorders for this device.

H. Patient Dissatisfaction

(Comment 14) There were 14 comments regarding the risk of patient dissatisfaction. These comments stated that patient dissatisfaction is infrequent and is only rarely the primary cause for reoperation. Additionally, many comments stated that patient dissatisfaction is the result of the patient having unrealistic expectations regarding the postimplantation appearance and function of his penis, and that this situation can be minimized by requiring thorough preoperative counseling regarding the realistic outcomes of device implantation. One physician comment stated that none of his patients had ever asked him to have a penile inflatable implant removed due to dissatisfaction.

FDA agrees that the majority of patients who receive penile inflatable implants report satisfaction with their device. Additionally, FDA concurs with the comments that patient dissatisfaction is typically the result of the patient having unrealistic expectations regarding the implant, and can be minimized by patient educational measures such as patient labeling and physician counseling. However, since patient dissatisfaction can ultimately require surgical intervention, FDA considers patient dissatisfaction a risk that should be addressed by manufacturers. Furthermore, since implantation of a penile inflatable implant may destroy any latent erectile capability the patient may have had, as well as make other, more conservative forms of treatment

for erectile dysfunction difficult or impossible, dissatisfied patients are left with few recourses. To assess and optimize the adequacy of information materials available to potential implant recipients, FDA believes it is essential to evaluate the frequency of this event and its consequences. Therefore, FDA believes it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence of patient dissatisfaction associated with the implantation of the penile inflatable implant.

I. Human Carcinogenicity

(Comment 15) Sixteen comments were received regarding the risk of human carcinogenicity. These comments stated that there is no evidence in the medical literature that the penile inflatable implant is associated with the development of cancer. Furthermore, nine of these comments were from physicians, who stated that they had not observed carcinogenicity in their personal experiences with these devices. One physician comment added that while carcinogenicity has not been proven to occur with the penile inflatable implant, further research is necessary to rule out this potential complication. Several comments stated that silicone causes solid state tumors in rodents, a phenomenon thought to be restricted to rodents and not applicable to humans. These comments also stated that epidemiological studies have not found that women with silicone breast implants, which contain silicone elastomers similar or identical to those used in the penile inflatable implant, are at an increased risk for cancer. Several comments stated that human carcinogenicity should be removed from the list of significant risks associated with the penile inflatable implant.

FDA believes that the potential carcinogenicity for this device remains unknown. The agency continues to believe that carcinogenicity is a potential risk that must be assessed in a PMA or PDP.

J. Human Reproductive and Teratogenic Effects

(Comment 16) There were 16 comments related to human reproductive and teratogenic effects. These comments stated that there is no evidence that the penile inflatable implant is teratogenic.

Nine comments from physicians stated that they had not observed reproductive and teratogenic effects in their personal experiences with these devices, one of whom added that further research is necessary to rule out this potential complication. Two comments stated that since most implant patients are beyond the age of fathering children, the risks of reproductive problems and teratogenic effects are not significant concerns. Furthermore, the small numbers of patients who do receive a device during their reproductive ages would not warrant a prospective study. Several comments stated that human reproductive and teratogenic effects should be removed from the list of significant risks associated with the penile inflatable implant.

FDA agrees that there are no published studies showing that penile inflatable implants are associated with toxic reproductive effects or teratogenic effects. However, FDA believes that the reproductive and/or teratogenic effects of these products remain potential risks that should be assessed in a PMA or PDP.

K. Immune Related Connective Tissue Disorders—Immunological Sensitization

(Comment 17) There were 16 comments regarding the risks of immune related connective tissue disorders and immunological sensitization. These comments stated that there is no evidence that the penile inflatable implant causes either immune related connective tissue disorders or immunological sensitization. Nine comments from physicians stated that they had not observed connective tissue disorders and other immunological effects in their personal experiences with these devices. Two comments stated that further research is necessary to rule out this potential complication. Several comments stated that no definitive link between silicone and autoimmune diseases has been established. Furthermore, several comments stated that since the diseases most frequently associated with autoimmune responses occur at a lower frequency in men than women, it may be impossible to extrapolate the findings from any study of silicone breast implants to the penile inflatable implant. Several comments stated that immune related connective tissue disorders and immunological sensitization should be removed from the list of significant risks associated with the penile inflatable implant.

FDA agrees that no definitive causal relationship has been established between immunological effects and/or connective tissue disorders and the penile inflatable implant. Epidemiological data published within the last several years (Refs. 3, 4, and 5) addressing the relationship between silicone breast prostheses and autoimmune diseases or connective tissue diseases indicate that silicone breast prostheses have not caused a large increase in the incidence of connective tissue disease in women with breast implants. However, the possibility of a smaller, increased risk of immunological effects among men with penile inflatable implants, or of an atypical, as yet undefined, syndrome or disease, cannot be eliminated based on these data. FDA is aware that differences in the incidence of such disorders between men and women make extrapolation of the results of breast implant studies to the outcome of the penile inflatable implant difficult. In the 1993 guidance document, FDA recommends that a cohort of penile inflatable implant recipients be regularly monitored for the occurrence of such adverse events as part of an active surveillance program for a minimum of 5 years postimplantation. FDA continues to believe that adverse immune related connective tissue disorders and immunological sensitization remain potential risks that must be assessed in a PMA or PDP, but FDA does not believe that 5 years of prospective data collection on a specific product will be necessary before PMA approval or PDP completion.

L. Biological Effects of Silica

(Comment 18) Five comments stated that fumed amorphous silica is so tightly bound in the silicone elastomer components of the penile inflatable implant that the fumed amorphous silica is biologically inactive. For that reason, these comments believed that the presence of fumed amorphous silica is not a risk to health of the penile inflatable implant. Two other comments stated that complications related to the release of silica from the penile inflatable implant have not been observed, although one of these comments added that further research is necessary to rule out this potential complication.

FDA does not believe there is sufficient information to eliminate fumed amorphous silica as a potential risk to health associated with the penile inflatable implant, particularly since the

amount of fumed amorphous silica is varied in order to achieve the desired physical characteristics of the device's components. Consequently, the agency believes that this potential risk to health should be addressed in a PMA or PDP.

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

(Comment 19) There were seven comments regarding the risk of silicone particle shedding. Four of these comments stated that small, but clinically insignificant, quantities of silicone particles have been noted in the periprosthetic tissues and inguinal lymph nodes of some penile inflatable implant recipients. Two comments stated that there is no evidence of silicone particle shedding from the penile inflatable implant. One comment stated that minimal, if any, silicone particle shedding occurs with this device. Several of these comments concluded that silicone particle shedding is not a risk of the penile inflatable implant.

Based upon information presented in the comments, FDA agrees that silicone particle shedding is not a risk to health of the penile inflatable implant. Although silicone particle shedding and subsequent migration have been reported with penile inflatable implants (Ref. 1), the quantity of such particles was minimal and no deleterious effects were associated with this finding. Furthermore, subsequent research published after the proposed call for PMA's and PDP's was unable to document evidence of silicone particle migration (Ref. 2). FDA, therefore, does not believe silicone particle shedding is a risk that needs to be addressed in PMA's or PDP's for these devices.

(Comment 20) Several comments stated that silicone gel leakage and migration are not risks to health of this device since there are no penile inflatable implants that contain silicone gel.

FDA disagrees with the comments that no penile inflatable implant contains silicone gel. As stated in response to comment 4 of this document, FDA is aware of at least one device model, no longer marketed in the United States, that contained silicone gel within its cylinder tip. FDA agrees with the comments that the potential risks of silicone gel leakage and migration are not applicable to penile inflatable implants that do not contain silicone gel.

N. Degradation of Polyurethane Elastomer

(Comment 21) There were three comments regarding the risk of polyurethane elastomer degradation. These comments stated that: (1) Currently marketed penile inflatable implants do not use polyurethane as a surface material, (2) in vitro testing regarding the degradation of polyurethane may not be predictive of degradation in vivo, and (3) there is no evidence in the literature of the release of either methylene diamine or toluene diamine in vivo from polyurethane.

FDA is aware of at least two penile inflatable implant models that have polyurethane elastomer as one of their surface materials; therefore, the agency does not agree with the comment that this material is not used. Furthermore, since the available information regarding the degradation of polyurethane elastomer is inconclusive, FDA does not believe there is sufficient information to eliminate it as a potential risk to health associated with the penile inflatable implant. Consequently, the agency believes that this potential risk to health should be addressed in a PMA or PDP. FDA believes that this potential risk is only applicable to penile inflatable implants that employ polyurethane elastomer as a surface, patient-contacting material.

O. Other Reported Complications

(Comment 22) Several comments were received regarding the "other reported complications" of the penile inflatable implant (i.e., hematoma, chronic pain, erythema, edema, ulceration, necrosis, scarring, and urinary retention). These comments stated that these complications either occur infrequently, are transient, or are not judged by patients or physicians to be severe.

FDA believes that insufficient information is available to determine the frequency of these events or their consequences. Therefore, FDA believes that it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence of all complications associated with the implantation of the penile inflatable implant.

P. Benefits of the Device

(Comment 23) Many comments were received regarding FDA's description of the benefit of the penile inflatable implant. Several comments objected to FDA's statement that "device implantation is a discretionary surgical procedure performed for reasons related to quality of life, rather than medical reasons." One comment stated that the benefits of the penile inflatable implant include penile reconstruction, in addition to quality of life improvement. This comment added that while many patients benefit with an improved quality of life, medical necessity and need are important indications for the use of penile inflatable implants. Another comment noted that the penile inflatable implant is, in fact, used to correct a medical problem—erectile dysfunction. A third comment argued that restoration of erectile function is analogous to surgical procedures to restore vision or hearing, or to salvage a limb, all of which could potentially be regarded as discretionary surgical procedures to improve quality of life.

Lastly, several comments stated that the benefits of the penile inflatable implant include improvement of quality of life, and the psychological benefits of the device should not be underestimated or undervalued. Furthermore, a comment from a penile inflatable implant recipient stated that the device impacts his "quality of life and manhood."

As stated in the proposed call for PMA's or PDP's, FDA believes that the penile inflatable implant is designed to provide sufficient penile rigidity to permit sexual intercourse. The proposed rule further states that this device is intended for the treatment of erectile dysfunction resulting from many medical conditions, such as diabetes mellitus, spinal cord injury, Peyronie's disease, and pelvic surgery. FDA continues to believe that device implantation is usually elective in nature, and the agency agrees with the comments that the primary benefit of the penile inflatable implant is restoration of erectile function. As noted by these comments, however, many implant recipients also benefit with an improved quality of life and FDA does not intend to underestimate or undervalue this benefit.

(Comment 24) Three comments objected to FDA's reference to improved fertility as being an intended benefit of the penile inflatable implant. One comment agreed with the April 1993 proposed rule, noting that a benefit of the device is the restoration of the ability for young men with erectile dysfunction to father children naturally.

FDA agrees that restoration of male fertility should not be listed as a benefit of the penile inflatable implant. Although this device may have provided an opportunity for a small number of patients to father children naturally, the agency acknowledges that this consequence of the device should not be listed as a benefit of the penile inflatable implant for the following reasons: (1) The primary reason for device implantation is the treatment of erectile dysfunction; (2) no penile inflatable implant manufacturer promotes their device with the claim of restoration of fertility; and (3) the majority of penile inflatable implant candidates are beyond the age of which they desire to father children. The agency's response to these comments is consistent with the recommendations provided at an April 15, 1993, meeting of the Gastroenterology and Urology Devices Advisory Panel.

Q. Need for Risk/Benefit Information

(Comment 25) Two comments objected to FDA's proposal that PMA's and PDP's analyze the prior treatment history and presurgical workup of penile inflatable implant recipients. They stated that it is physicians, in consultation with patients, who should decide the choice of treatment for erectile dysfunction, and that devices should not be treated any differently in this respect than pharmaceuticals where a physician has many different drugs available to treat a disorder and chooses the appropriate one based on the patient's needs.

FDA agrees that it should not interfere with the practice of medicine. However, the agency believes that manufacturers have a responsibility to report the circumstances of use of their device in the product's labeling, especially due to the potential for irreversible effects following implantation of a penile inflatable implant. Consequently, FDA believes that information regarding the prior treatment history and presurgical workup of penile inflatable implant recipients should

be reported in a PMA or PDP to ensure that labeling for the product will provide reasonable assurance of safe and effective use.

(Comment 26) Three comments stated that quality of life and psychological evaluations are not useful to judge the effectiveness of the penile inflatable implant since the primary goal of device implantation is restoration of erectile function. Two of these comments added that: (1) Manufacturers do not make claims regarding psychological benefit, (2) it is inappropriate for FDA to require a manufacturer to demonstrate this benefit, (3) there are no accepted tests for measuring the psychological impact of the penile inflatable implant, and (4) existing tests for psychological well-being and self-esteem are confounded by multiple life variables, including the patient's and partner's general health, sexual functioning, and understanding of the potential complications when making the decision to have a penile inflatable implant. One comment stated that assessment of psychological benefit would likely require large clinical studies.

FDA agrees that the primary benefit derived from implantation of a penile inflatable implant is restoration of erectile function. However, FDA continues to believe that the potential quality of life and psychological benefits offered by the device are important, albeit secondary, components of the device's effectiveness. Although FDA agrees that designing studies to assess the psychological benefit of implantation with a penile inflatable implant may be difficult, FDA believes the psychological impact of the device can and should be assessed in a PMA or PDP as a secondary effectiveness measure. The agency will accept a variety of types of scientific evidence in support of a PMA or PDP, as long as the data constitute valid scientific evidence within the meaning of 21 CFR 860.7(c)(2) (e.g., a validated quality of life patient questionnaire can provide data to address this issue).

R. PMA Contents

(Comment 27) FDA received two extensive comments on the types of manufacturing information, preclinical testing, and clinical data that should be required in a PMA for a penile inflatable implant, as well as several general comments on the appropriate contents of a PMA.

Additionally, FDA received one comment proposing detailed modifications to the quality of life, satisfaction, and psychological evaluation recommendations stated in the proposed call for PMA's and PDP's.

FDA agrees with many of the points raised in these comments. Although the 1993 guidance document describes the general types of manufacturing, preclinical, and clinical data that FDA believes can support approval of a PMA for a penile inflatable implant, the agency realizes that other, scientifically sound methods exist for addressing the identified risks and benefits of the device and encourages manufacturers to document the safety and effectiveness of their device using the least burdensome approaches. In fact, FDA has agreed to the use of many of these alternative approaches for the collection and analysis of data in its past interactions with penile inflatable implant manufacturers. Furthermore, FDA intends to revise the 1993 guidance document to incorporate many of these comments.

III. Findings With Respect to Risks and Benefits

A. Degree of Risk

1. Infection

Infection is a risk associated with any surgical implant procedure, including the penile inflatable implant. Compromised device sterility and surgical techniques may be a major contributing factor to this risk. Infection may result in the removal of the implant and may result in an inability to replace the device due to corporeal fibrosis and scarring.

2. Migration and Extrusion

Migration refers to the movement of the components of the penile inflatable implant within the body. In some cases, a portion of the implant migrates externally (''extrusion''). The cylinders and pump can migrate either proximally or distally, leading to inadequate support of the glans penis, difficulty in manipulating the pump, or pressure necrosis with subsequent erosion. Extrusion

is usually associated with wound dehiscence at the site of incision, but can also occur secondary to erosion. Factors contributing to migration and extrusion include implantation of a device that is too large, iatrogenic injury to the surrounding tissues, and infection. Migration and extrusion of the penile inflatable implant can lead to surgical intervention.

3. Erosion

Erosion is the breakdown of tissue adjacent to the device. The cylinders can erode through the distal urethra, the pump can erode through the scrotal wall, and, rarely, the reservoir can erode through the bladder or bowel. Factors contributing to erosion include implantation of a device that is too large, iatrogenic injury to the surrounding tissues, and infection. Erosion may lead to device extrusion, and can require surgical intervention.

4. Fibrous Capsular Formation

The formation of a fibrous capsule around the components of the penile inflatable implant is a risk associated with this device. Fibrous capsule formation around the reservoir and/or pump may either cause spontaneous inflation of the cylinders or prevent the cylinders from completely deflating. Significant fibrous capsular formation may be corrected by device manipulation, corrective surgery, or surgical removal of the device and adjacent tissues. The effects of fibrous capsule formation vary from reduced satisfaction with the implant to explantation.

5. Mechanical Malfunctions

As with other prosthetic devices intended to restore a physiologic function, penile inflatable implants may mechanically malfunction. Reported types of mechanical malfunctions include leakage, cylinder rupture, cylinder aneurysm, spontaneous inflation/deflation, tubing kinks, and pump valve failure. Mechanical malfunctions may be caused by improper device handling or improper surgical technique, or problems with the device's design or manufacturing process. Surgical intervention to remove or replace the device is required if the patient desires a functional prosthesis.

6. Iatrogenic Disorders

Improper device handling, inadequate or vigorous dilatation, aggressive dissection, malpositioning of the device, cylinder suturing, and cylinder missizing are among the preventable complications caused as a result of surgical technique. Iatrogenic disorders may be responsible for various adverse conditions necessitating device removal and/or replacement.

7. Patient Dissatisfaction

If patients are not provided information and counseling regarding the risks and benefits of the penile inflatable implant prior to implantation, they may not have realistic expectations of the physical, psychological, and functional outcomes of the device. Uninformed patients may be dissatisfied with the device due to complications such as unresolved pain, as well as disappointment in cosmetic appearance, concealability, rigidity/firmness, and penile sensation. Some dissatisfied patients have elected to have the device surgically removed because the implant did not meet their expectations.

8. Human Carcinogenicity

The potential for developing cancer as a result of the long-term implantation of the penile inflatable implant cannot be eliminated as a potential risk associated with this device.

9. Human Reproductive and Teratogenic Effects

Although FDA is not aware of data indicating that the penile inflatable implant is associated with reproductive and teratogenic effects, the potential for teratogenicity and other reproductive adverse effects as a result of long-term implantation of the device cannot be eliminated as a possible risk to health.

10. Immune Related Connective Tissue Disorders—Immunological Sensitization

The potential for developing immunological effects and/or connective tissue disorders as a result of long-term exposure to the penile inflatable implant remains uncertain. Since the publication

of the proposed rule 6 years ago, new epidemiological data (Refs. 3, 4, and 5) addressing the relationship between silicone breast prostheses and autoimmune diseases or connective tissue diseases indicate that silicone breast prostheses have not caused a large increase in the incidence of connective tissue disease in women with breast implants. However, the possibility of a smaller, increased risk of immunological effects among men with penile inflatable implants, or of an atypical, as yet undefined, syndrome or disease, cannot be eliminated based on these data.

11. Biological Effects of Silica

Amorphous fumed silica is bound to the silicone in the elastomer of the penile inflatable implant. Silica presents a potential risk which should be addressed in a PMA or PDP.

12. Silicone Gel Leakage and Associated Migration

Small quantities of silicone gel are present in at least one model of penile inflatable implant. Silicone gel leakage and associated migration are potential risks which should be addressed in a PMA or PDP for any device that contains this material.

13. Degradation of Polyurethane Elastomer

Polyurethane elastomer materials, which have been used as surface materials in some penile inflatable implants, may degrade over time and release degradation products which are potential carcinogens in animals. When present, polyurethane elastomer degradation is a potential risk that should be addressed in a PMA or PDP.

14. Other Reported Complications

Other reported complications associated with implantation of the penile inflatable implant include hematoma, chronic pain, erythema, edema, ulceration, necrosis, scarring, and urinary retention, which should be addressed in a PMA or PDP.

B. Benefits of the Device

The penile inflatable implant is intended to restore the ability to have an erection in men with erectile dysfunction. It has the potential to be an effective treatment for erectile dysfunction. Implant recipients may also benefit from an improved quality of life.

IV. Final Rule

Under section 515(b)(3) of the act, FDA is adopting the findings as published in the preamble to the April 1993 proposed rule and is issuing this final rule to require premarket approval of the generic type of device, the penile inflatable implant, by revising § 876.3350(c).

Under the final rule, a PMA or a notice of completion of a PDP is required to be filed on or before [*insert date 90 days after date of publication in the Federal Register*], for any penile inflatable implant that was in commercial distribution before May 28, 1976, or that has been found by FDA to be substantially equivalent to such a device on or before [*insert date 90 days after date of publication in the Federal Register*]. An approved PMA or a declared completed PDP is required to be in effect for any such device on or before 180 days after FDA files the application.

Any other penile inflatable implant that was not in commercial distribution before May 28, 1976, or that has not been found by FDA to be substantially equivalent to such a device on or before [*insert date 90 days after date of publication in the Federal Register*], is required to have an approved PMA or a declared completed PDP in effect before it may be marketed.

If a PMA or a notice of completion of a PDP for a penile inflatable implant is not filed on or before the 90th day past the effective date of this regulation, that device will be deemed adulterated under section 501(f)(1)(A) of the act (21 U.S.C. 351(f)(1)(A)), and commercial distribution of the device will be required to cease immediately. The device may, however, be distributed for investigational use, if the requirements of the investigational device exemption (IDE) regulations (part 812) (21 CFR part 812) are met.

Under § 812.2(d) of the IDE regulations, FDA hereby stipulates that, on the effective date of this rule, the exemptions from the IDE requirements in § 812.2(c)(1) and (c)(2) will no longer

apply to clinical investigations of the penile inflatable implant. Further, FDA concludes that investigational penile inflatable implants are significant risk devices as defined in § 812.3(m) and advises that, as of the effective date of this rule, the requirements of the IDE regulations regarding significant risk devices will apply to any clinical investigation of a penile inflatable implant. For any penile inflatable implant that is not the subject of a timely filed PMA or PDP, an IDE must be in effect under § 812.20 on or before 90 days after the effective date of this regulation or distribution of the device must cease. FDA advises all persons presently sponsoring a clinical investigation involving the penile inflatable implant to submit an IDE application to FDA no later than 60 days after the effective date of this final rule to avoid the interruption of ongoing investigations.

V. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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.

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. The Office of Management and Budget (OMB) has determined that this final rule is a significant regulatory action subject to review under the Executive Order.

FDA expects that only two manufacturers will submit a PMA or PDP for the penile inflatable implant. FDA does not believe that two companies are a significant number of small entities. FDA estimates that it costs up to \$1 million to develop and submit a PMA or PDP for this type of device. As noted previously, the penile inflatable implant was classified into class III on November 23, 1983, and FDA published a proposed rule to require a PMA or PDP for this device on April 28, 1993. Thus, manufacturers have long been aware of the need to develop information in support of a PMA or a PDP. The cost of developing the data, therefore, has been spread over the past several years. Moreover, since the publication of the proposed rule, FDA has been working closely with both manufacturers to assist them in preparing for the submission of a PMA or a PDP, and one has successfully completed a PDP for two device models. FDA estimates based on such information as is publicly available, that these two companies have annual revenues in excess of several hundred million dollars. FDA, therefore, believes that this final rule will not be an undue burden on these manufacturers. The agency therefore certifies that the final 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.

VII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3530). The burden hours required for § 876.3350(c) are reported and approved under OMB Control No. 0910-0231.

VIII. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. These references may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

1. Barrett, D. M., D. C. O'Sullivan, A. A. Maliza, H. M. Reiman, and P. C. Abell-Aleff, "Particle Shedding and Migration From Silicone Genitourinary Prosthetic Devices," *The Journal of Urology*, 146:319-322, 1991.
2. Fishman, I. J. and F. N. Flores, "Retrospective Review of Pelvic Lymph Nodes in Patients with Previously Implanted Silicone Penile Prosthesis," *The Journal of Urology*, 149:355A, 1993.
3. Hennekens, C. H., I. Lee, N. Cook, P. R. Hebert, E. W. Karlson, F. LaMotte, J. E. Manson, and J. E. Buring, "Self-reported Breast Implants and Connective-Tissue Diseases in Female Health Professionals," *Journal of the American Medical Association*, 275:616-621, 1996.
4. Silverman, B. G., S. L. Brown, R. A. Bright, R. G. Kaczmarek, J. B. Arrowsmith-Lowe, and D. A. Kessler, "Reported Complications of Silicone Gel Breast Implants: An Epidemiologic Review," *Annals of Internal Medicine*, 124:744-756, 1996.
5. Institute of Medicine, "Safety of Silicone Breast Implants," National Academy Press, Washington, DC, 1999.

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, 21 CFR part 876 is amended as follows:

PART 876—GASTROENTEROLOGY—UROLOGY DEVICES

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

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Section 876.3350 is amended by revising paragraph (c) to read as follows:

§ 876.3350 Penile inflatable implant.

* * * * *

(c) *Date premarket approval application (PMA) or notice of completion of a product development protocol (PDP) is required.* A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before *[insert date 90 days after date of publication in the **Federal Register**]*, for any penile inflatable implant that was in commercial distribution before May 28, 1976, or that has, on or before *[insert date 90 days after date of publication in the **Federal Register**]*, been found to be substantially equivalent to a penile inflatable



implant that was in commercial distribution before May 28, 1976. Any other penile inflatable implant shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.

Dated: 3/24/00
March 24, 2000

Linda S. Kahan

Linda S. Kahan
Deputy Director for Regulations Policy
Center for Devices and Radiological Health

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

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