in financial statements to deceive financial statement users.''[42] SAS 82 further states that fraudulent financial reporting may involve falsification or alteration of accounting records; misrepresenting or omitting events, transactions or other information in the financial statements; and the intentional misapplication of accounting principles relating to amounts, classifications, the manner of presentation, or disclosures in the financial statements.[43] The clear implication of SAS 82 is that immaterial misstatements may be fraudulent financial reporting.[44]

Auditors that learn of intentional misstatements may also be required to (1) re-evaluate the degree of audit risk involved in the audit engagement, (2) determine whether to revise the nature, timing, and extent of audit procedures accordingly, and (3) consider whether to resign.[45]

Intentional misstatements also may signal the existence of reportable conditions or material weaknesses in the registrant's system of internal accounting control designed to detect and deter improper accounting and financial reporting.[46] As stated by the National Commission on Fraudulent Financial Reporting, also known as the Treadway Commission, in its 1987 report,

> The tone set by top management—the corporate environment or culture within which financial reporting occurs—is the most important factor contributing to the integrity of the financial reporting process. Notwithstanding an impressive set of written rules and procedures, if the tone set by management is lax, fraudulent financial reporting is more likely to occur.[47]

An auditor is required to report to a registrant's audit committee any reportable conditions or material weaknesses in a registrant's system of internal accounting control that the auditor discovers in the course of the examination of the registrant's financial statements.[48]

GAAP Precedence Over Industry Practice

Some have argued to the staff that registrants should be permitted to follow an industry accounting practice even though that practice is inconsistent with authoritative accounting literature. This situation might occur if a practice is developed when there are few transactions and the accounting results are clearly inconsequential, and that practice never changes despite a subsequent growth in the number or materiality of such transactions. The staff disagrees with this argument. Authoritative literature takes precedence over industry practice that is contrary to GAAP.[49]

General Comments

This SAB is not intended to change current law or guidance in the accounting or auditing literature.[50] This SAB and the authoritative accounting literature cannot specifically address all of the novel and complex business transactions and events that may occur. Accordingly, registrants may account for, and make disclosures about, these transactions and events based on analogies to similar situations or other factors. The staff may not, however, always be persuaded that a registrant's determination is the most appropriate under the circumstances. When disagreements occur after a transaction or an event has been reported, the consequences may be severe for registrants, auditors, and, most importantly, the users of financial statements who have a right to expect consistent accounting and reporting for, and disclosure of, similar transactions and events. The staff, therefore, encourages registrants and auditors to discuss on a timely basis with the staff proposed accounting treatments for, or disclosures about, transactions or events that are not specifically covered by the existing accounting literature.

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[42] AU § 316.04. See also AU § 316.03. An unintentional illegal act triggers the same procedures and considerations by the auditor as a fraudulent misstatement if the illegal act has a direct and material effect on the financial statements. See AU § § 110 n. 1, 316 n. 1, 317.05 and 317.07. Although distinguishing between intentional and unintentional misstatements is often difficult, the auditor must plan and perform the audit to obtain reasonable assurance that the financial statements are free of material misstatements in either case. See AU § 316 note 3.

[43] AU § 316.04. Although the auditor is not required to plan or perform the audit to detect misstatements that are immaterial to the financial statements, SAS 82 requires the auditor to evaluate several fraud ''risk factors'' that may bring such misstatements to his or her attention. For example, an analysis of fraud risk factors under SAS 82 must include, among other things, consideration of management's interest in maintaining or increasing the registrant's stock price or earnings trend through the use of unusually aggressive accounting practices, whether management has a practice of committing to analysts or others that it will achieve unduly aggressive or clearly unrealistic forecasts, and the existence of assets, liabilities, revenues, or expenses based on significant estimates that involve unusually subjective judgments or uncertainties. See AU § § 316.17*a* and .17*c*.

[44] AU §§ 316.34 and 316.35, in requiring the auditor to consider whether fraudulent misstatements are material, and in requiring differing responses depending on whether the misstatement is material, make clear that fraud can involve immaterial misstatements. Indeed, a misstatement can be ''inconsequential'' and still involve fraud.

Under SAS 82, assessing whether misstatements due to fraud are material to the financial statements is a ''cumulative process'' that should occur both during and at the completion of the audit. SAS 82 further states that this accumulation is primarily a ''qualitative matter'' based on the auditor's judgment. AU § 316.33. The staff believes that in making these assessments, management and auditors should refer to the discussion in Part 1 of this SAB.

[45] AU §§ 316.34 and 316.36. Auditors should document their determinations in accordance with AU § § 316.37, 319.57, 339, and other appropriate sections.

[46] *See, e.g.,* AU § 316.39.

[47] Report of the National Commission on Fraudulent Financial Reporting at 32 (October 1987). *See also* Report and Recommendations of the Blue Ribbon Committee on Improving the Effectiveness of Corporate Audit Committees (February 8, 1999).

[48] AU § 325.02. *See also* AU § 380.09, which, in discussing matters to be communicated by the auditor to the audit committee, states, ''The auditor should inform the audit committee about adjustments arising from the audit that could, in his judgment, either individually or in the aggregate, have a significant effect on the entity's financial reporting process. For purposes of this section, an audit adjustment, whether or not recorded by the entity, is a proposed correction of the financial statements. . . .''

[49] *See* AU § 411.05.

[50] The FASB Discussion Memorandum, *Criteria for Determining Materiality*, states that the financial accounting and reporting process considers that ''a great deal of the time might be spent during the accounting process considering insignificant matters . . . . If presentations of financial information are to be prepared economically on a timely basis and presented in a concise intelligible form, the concept of materiality is crucial.''

This SAB is not intended to require that misstatements arising from insignificant errors and omissions (individually and in the aggregate) arising from the normal recurring accounting close processes, such as a clerical error or an adjustment for a missed accounts payable invoice, always be corrected, even if the error is identified in the audit process and known to management. Management and the auditor would need to consider the various factors described elsewhere in this SAB in assessing whether such misstatements are material, need to be corrected to comply with the FCPA, or trigger procedures under Section 10A of the Exchange Act. Because this SAB does not change current law or guidance in the accounting or auditing literature, adherence to the principles described in this SAB should not raise the costs associated with recordkeeping or with audits of financial statements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. 91N–0281]

RIN 0910–AZ17

General and Plastic Surgery Devices; Effective Date of Requirement for Premarket Approval of the Silicone Inflatable Breast Prosthesis

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 silicone inflatable breast prosthesis, a generic type of medical device intended to augment or reconstruct the female breast. This device is made of a silicone shell that is inflated with sterile isotonic saline. Commercial distribution of this device must cease unless a manufacturer or importer has filed with FDA a PMA or PDP for its version of the silicone inflatable breast prosthesis within 90 days of the effective date of this regulation. 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.

EFFECTIVE DATE: August 18, 1999.

FOR FURTHER INFORMATION CONTACT: Stephen P. Rhodes, Center for Devices and Radiological Health (HFZ–410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–3090.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of June 24, 1988 (53 FR 23856), FDA published a final rule classifying into class III (premarket approval) the silicone inflatable breast prosthesis, a medical device. Section 878.3530 (21 CFR 878.3530) of FDA's regulations setting forth the classification of the silicone inflatable breast prosthesis applies to: (1) Any silicone inflatable breast prosthesis that was in commercial distribution before May 28, 1976, and (2) any device that FDA has found to be substantially equivalent to a silicone inflatable breast prosthesis in commercial distribution before May 28, 1976.

In an advanced notice of proposed rulemaking published in the **Federal Register** of January 6, 1989 (54 FR 550), the agency identified the silicone inflatable breast prosthesis as one of the high-priority devices that would be subject to PMA or PDP requirements. FDA issued a notice in the **Federal Register** of September 26, 1991 (56 FR 49098), requiring manufacturers to disseminate information on risks associated with the silicone gel-filled breast prosthesis and the silicone inflatable breast prosthesis. FDA stated that either type of breast prosthesis would be misbranded under the act if its labeling did not provide adequate information for patients.

In the **Federal Register** of January 8, 1993 (58 FR 3436), 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 silicone inflatable breast prosthesis and all substantially equivalent devices. 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 silicone inflatable breast prosthesis was required to be submitted by January 25, 1993. The comment period initially closed on March 6, 1993. In the **Federal Register** of March 10, 1993 (58 FR 13230), FDA extended the comment period for 30 days to April 8, 1993, to ensure that there was adequate time for preparation and submission of comments on the proposed rule.

The agency received 134 comments in response to the January 8, 1993, proposed rule. These comments were from individuals, manufacturers, professional societies, and consumer and health groups. Most of the comments supported the proposed rule.

In the **Federal Register** of June 28, 1995 (60 FR 33608), FDA issued a notice announcing the availability of an updated patient risk information booklet, entitled ''Information for Women Considering Saline-filled Breast Implants.'' The information booklet provided prospective patients with information about possible risks involved with silicone inflatable breast prostheses. FDA gave the updated information booklet to the manufacturers of saline-filled breast implants (silicone inflatable breast prostheses) to include with their labeling. FDA intended that physicians who perform breast implant surgery give this information to their patients as they considered implantation of a silicone inflatable breast prosthesis.

FDA is aware that new information on the device has become available since the proposed rule was published in January 1993. On June 2, 1999, the Institute of Medicine (IOM) released a comprehensive review of the published literature and ongoing studies on both saline-filled and silicone gel-filled breast implants entitled ''Safety of Silicone Breast Implants.'' Both of these types of implants have a silicone elastomer shell. The IOM made a clear distinction between local complications and systemic health concerns. The IOM determined that there was insufficient evidence to establish that breast implants cause systemic health effects such as autoimmune disease. The IOM concluded that there is ''no definitive evidence linking breast implants to cancer, immunological diseases, neurological problems, or other systemic diseases. On the basis of our committee's review of the data, we concluded that women with breast implants are no more likely than other women to develop these systemic illnesses.'' However, the IOM also concluded that local complications are ''the primary safety issue with silicone breast implants.'' These local complications include rupture, pain, capsular contracture, disfigurement, and serious infection, which may lead to medical interventions and repeat surgeries. The agency believes that local complications should be addressed in a PMA or PDP submission. Therefore, while it is possible that the level of risk presented by the device may differ somewhat from that described in the proposal, FDA nevertheless believes that the risks to health identified in the proposed rule still exist for the device and consequently, should be addressed in PMA's or PDP's for the device.

This regulation is final upon publication and requires PMA's or notices of completion of a PDP for all silicone inflatable breast prostheses classified under § 878.3530 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 silicone gel-filled breast prosthesis (21 CFR 878.3540).

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

A. General Comments

1. FDA received comments from 116 women consumers and six health professionals supporting the proposed call for PMA's or PDP's. Sixty-four of the women consumers were reconstruction or augmentation patients who were dissatisfied with their implants. These women believed that their breast implants have caused them adverse health effects. Fourteen of these breast implant recipients provided medical histories and patient records to support their belief that their illnesses are associated with their breast implants. Seven other comments also expressed the belief that breast prostheses cause adverse health effects. The other 43 women did not indicate whether or not they had been implanted with breast implants. Nineteen of these 43 comments recommended that silicone inflatable breast prostheses be recalled and banned until long-term safety and effectiveness studies are completed. Some comments recommended that silicone gel-filled breast prostheses be recalled and banned. Thirty-one women expressed strong opinions that the risks associated with all breast implants are unacceptable.

FDA does not believe that the available evidence supports a conclusion that either banning or recalling the device would be appropriate. Rather, FDA believes that requiring the submission of PMA's or PDP's for the silicone inflatable breast prosthesis will provide FDA an opportunity to assess more fully the risks and benefits of these devices in order to determine whether there is reasonable assurance of their safety and effectiveness, or absent such an assurance what regulatory course should be taken.

The comments addressing the silicone gel-filled breast implant are not within the scope of this rule. In the **Federal Register** of April 10, 1991 (56 FR 14620), FDA issued a final rule requiring the submission of PMA's or PDP's for the silicone gel-filled breast prosthesis.

2. One comment stated that PMA's or PDP's are not necessary for this device because adequate studies on silicone toxicity already exist establishing the safety and effectiveness of the silicone inflatable breast prosthesis. This comment stated that the extensive published research has not found any causal relationship between silicone-containing breast prostheses and the adverse events observed in some women with these devices. Other comments stated that existing information on the silicone gel-filled breast prosthesis and on other types of silicone-containing prostheses in use (the chin prosthesis (21 CFR 878.3550); the ear prosthesis (21 CFR 878.3590), and the finger joint prosthesis (21 CFR 888.3230)) provide adequate information to support the safety and effectiveness of the silicone inflatable breast prosthesis.

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 establish the safety and effectiveness of the silicone inflatable breast prosthesis. FDA will consider all information contained in PMA's or PDP's in determining whether there is reasonable assurance of the safety and effectiveness of these devices.

3. Four comments suggested that additional guidance on the data requirements for PMA's be made available before publishing the final rule. One of these comments also requested an open dialogue between FDA, the industry, and the scientific and medical communities to develop a consensus on the preclinical and clinical data necessary to establish the safety and effectiveness of the device, and reissuance of the proposed rule with a longer timeframe.

The 1993 proposed rule provided guidance on the appropriate data to be included in the PMA for the silicone inflatable breast prosthesis. Although section 515(b) of the act does not require the agency to provide specific guidance on the contents of specific PMA's, FDA has issued a ''Draft Guidance for the Preparation of PMA Application for Silicone Inflatable (Saline) Breast Prostheses'' in November 1994 and a revised draft guidance in January 1995 (the 1995 guidance document). The 1995 guidance document is available from the internet at ''www.fda.gov/cdrh/ode/odegr532.html''. In order to receive the ''Draft Guidance for Silicone Inflatable (Saline) Breast Prostheses'' via your fax machine, call CDRH Facts-On-Demand (FOD) system at 800–899–0381 or 301–827–0111 from a touch-tone telephone. At the first voice prompt press 1 to access DSMA Facts, at the second voice prompt press 2, and then enter the document number (223) followed by the pound sign (#). Follow the remaining voice prompts to complete you request.

In June 1996, FDA sent known manufacturers of the silicone inflatable breast prosthesis a letter describing the recommended data for a PMA. The period of time between the classification of the device in 1988 and the date by which PMA's must be filed is more than 10 years. Thus, FDA believes that sufficient time and guidance has been provided to allow sponsors to develop the data for a PMA submission. FDA agrees that dialogue with industry and with the scientific and medical community is important; FDA staff have been and continue to be accessible to discuss PMA and PDP content information with industry and the scientific and medical community.

4. Two comments suggested that postapproval studies could be used to support approval of the silicone inflatable breast prosthesis, and another comment suggested the use of FDA's postmarket surveillance authority.

FDA notes that, by definition, postapproval studies are studies performed after the approval of a PMA and that postmarket surveillance studies are studies used to acquire additional performance information about a device already determined to be reasonably safe and effective. In the 1993 proposed rule, FDA stated that postapproval studies would be required to fully assess the potential carcinogenicity and teratogenicity of any approved silicone inflatable breast prostheses. In the 1995 guidance document, FDA restated this need for postapproval studies and added that postapproval studies would also be needed to assess the potential for causing adverse immunological effects and/or connective tissue disorders.

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 devices 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. Evidence that constitutes valid scientific evidence within the meaning of § 860.7(c)(2) (21 CFR 860.7(c)(2)) may be submitted in support of a PMA or PDP, but it will remain the agency's judgment whether the submitted evidence provides reasonable assurance of safety and effectiveness.

6. Six comments stated that tissue expanders should be not be included in the call for PMA's or PDP's. Five comments said that tissue expanders intended for short-term use are unclassified devices. One comment

suggested that the tissue expander intended for short-term use should be classified into class II and that the tissue expander intended for long-term use should be classified into class III.

Saline-filled silicone tissue expanders are used for general surgical procedures, as well as for breast implantation surgery. FDA agrees that tissue expanders intended for short-term use or for general surgical purposes are unclassified devices and are not covered in this final rule. FDA plans to initiate classification procedures for that device at a future date. However, saline inflatable tissue expanders that meet the definition of a silicone inflatable breast prosthesis are included in this final rule.

7. One comment said the risk section should be rewritten because it reflects an agency bias against the silicone inflatable breast prosthesis, in that it equates the risks associated with the silicone inflatable breast prosthesis with those of the silicone gel-filled breast prosthesis.

FDA disagrees. The preamble to the proposed rule clearly states that much of the literature cited in the risk section of the proposed rule referred specifically to the silicone inflatable breast prosthesis. The agency cited information about other silicone devices only where there was no documentation specific to the silicone inflatable breast prosthesis. Comparison of risk information between devices should not be confused with an equation of risk.

B. Fibrous Capsular Contraction

8. There were six comments on the risk of fibrous capsular contracture. These comments indicated that fibrous capsule formation occurs around any implanted device and that this is part of the healing process. They stated that, although this risk to health is a frequent outcome, it is not life-threatening, and should be considered a relatively minor risk to health.

FDA agrees that fibrous capsular contracture is usually not life-threatening and that normal fibrous capsule formation is part of the wound healing process after the implantation of any prosthesis. Fibrous capsular contracture, however, is associated with clinical changes ranging from a nearly imperceptible deformation of the implant to marked distortion and firmness, often accompanied by tenderness, pain, and discomfort. Significant fibrous capsular contracture, Baker grades 3 and 4, may require surgical removal of the device, making contracture a serious risk to health. As stated in the 1995 guidance document, FDA is requesting time-course data on the rate and frequency of fibrous capsular contracture.

C. Deflation

9. There were seven comments on the risk of deflation. Two comments said that deflation is not life-threatening, two characterized deflation as being of low or no risk, and three said it is infrequent.

FDA agrees that this risk to health is not life-threatening. However, deflation of the silicone inflatable breast prosthesis eliminates the benefit of the device. In addition, the recipient may then elect to have her implant surgically explanted and have a second breast prosthesis implanted. This additional surgery makes deflation a potentially serious adverse event. As noted in the 1995 guidance document, FDA requested information to address the incidence of deflation and rupture for this device.

D. Infection

10. Four comments stated that the incidence of infection associated with the implantation of silicone inflatable breast prostheses is not any higher than it is for other implantation surgeries. One comment said that FDA needs an accurate determination of the incidence of infection in women implanted with silicone inflatable breast prostheses.

FDA believes that it is important for studies submitted in a PMA or PDP to provide accurate information on the incidence of infection associated with the implantation of the silicone inflatable breast prosthesis.

E. Interference With Early Tumor Detection

11. Several comments stated that mammography may be more difficult to perform and that it may be less effective for the early detection of tumors in women with breast implants. Two other comments disagreed, stating that there are no data showing that the presence of breast implants has hindered or delayed the detection of breast tumors. The same comments stated that implantation of the device under the pectoralis muscles may reduce the interference with mammography, that interference can be overcome with special detection procedures, and that cancer detection does not rely solely on mammography.

FDA agrees that the presence of a silicone inflatable breast prosthesis may interfere with the standard mammography procedures used to screen patients for breast cancer. The device may produce a shadow on the radiograph that obscures visualization of a significant portion of the breast. In addition, the prosthesis compresses overlying breast tissue, reducing contrast and making mammographic assessment more difficult. Mammography of the augmented or reconstructed breast requires special techniques, which may result in increased exposure to radiation. Even under the best of circumstances, silicone inflatable breast prostheses are likely to limit the effectiveness of this examination for breast cancer detection. As stated in the 1995 guidance document, FDA is requesting information on the potential interference of the silicone inflatable breast prosthesis on the ability of mammography to detect tumors in breast tissue.

F. Human Carcinogenicity

12. Nine comments said that there is no established correlation between cancer and women with a silicone inflatable breast prosthesis. They stated that silicone causes solid state tumors in rodents, a phenomenon thought to be restricted to rodents and not applicable to humans. They also stated that epidemiological studies have not found that women with breast implants are at an increased risk for cancer.

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.

G. Human Teratogenicity

13. There were five comments related to human teratogenicity. Three comments stated that there is no evidence that the silicone inflatable breast prosthesis is teratogenic. Two comments stated that teratogenicity is a remote risk, which could be addressed in postapproval studies. One comment stated that seven studies published between 1975 and 1993 (including the literature FDA cited in the proposed rule), in conjunction with the absence of reports of defects among children born to women who have undergone mammary augmentation/reconstruction with silicone implants, indicates that teratogenicity is not an identified or a potential risk to health.

FDA agrees that there are no published studies showing that silicone inflatable prostheses are associated with toxic reproductive effects or teratogenic effects. However, FDA believes that teratogenicity and/or reproductive effects of silicone elastomers remain potential risks that should be assessed in a PMA or PDP. This information was requested in the proposed rule and in the 1995 guidance document.

H. Adverse Immunological Effects and/or Connective Tissue Disorders

14. Five comments stated that no definitive link between silicone and autoimmune diseases has been established. These comments stated that the incidence of these diseases in women with breast implants is no higher than it is in women without breast implants. Two of these comments suggested that some women may be more genetically susceptible to the immunological effects than others. As stated previously, 71 consumer comments expressed the belief that breast implants cause unacceptable adverse health effects. One physician reported that his patients with breast prostheses had a higher than expected prevalence of positive antinuclear antibody (ANA) test results. Because there was no difference in the ANA test results between patients with gel-filled and saline-filled breast prostheses, this comment attributed the positive ANA results for both patient populations to the silicone shell of the prostheses.

FDA agrees that no definitive causal relationship has been established between immunological effects and/or connective tissue disorders and the silicone inflatable breast prosthesis. FDA is aware of the concerns expressed in the consumer comments. FDA also recognizes that a positive ANA test without clinical symptoms is a nonspecific finding. In the 1995 guidance document, FDA recommended that recipients of silicone inflatable breast prostheses be regularly monitored for the occurrence of such adverse events for a minimum of 10 years postimplantation. FDA continues to believe that adverse immunological effects and/or connective tissue disorders remain potential risks that must be assessed in a PMA or PDP, but FDA does not believe that 10 years of prospective data collection on a specific product will be necessary to do so.

I. Calcification

15. Several comments stated that calcification is not life-threatening and is of unknown clinical significance. Other comments suggest that calcification: (1) May occur in as many as 25 percent of breast implant patients; (2) is rare; (3) is closely associated with capsular contracture; (4) may complicate the interpretation of mammograms; and (5) may cause abrasions of the silicone shell of the device if the calcium salt crystals have sharp edges, making the implant more susceptible to rupture.

FDA believes that there is not much information on the incidence and effects of calcification in women implanted with silicone inflatable breast prostheses. FDA believes that calcification remains an uncharacterized potential risk to health. Consequently, as stated in the proposed rule, FDA believes that PMA's or PDP's for this device should include time-course information on the incidence of calcification.

J. Biological Effects of Silica

16. Several comments stated that fumed amorphous silica is so tightly bound in the silicone elastomer shell of the silicone inflatable breast prosthesis 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 silicone inflatable breast prosthesis.

FDA does not believe there is sufficient information to eliminate fumed amorphous silica as a potential risk to health associated with the silicone inflatable breast prosthesis, particularly since the amount of fumed amorphous silica is varied in order to achieve the desired physical characteristics of the shell. Consequently, the agency believes that this potential risk to health should be addressed in a PMA or PDP.

K. Interference With Breast Feeding

17. Several comments stated that the presence of the silicone inflatable breast prosthesis could potentially interfere with the breast feeding of infants. The comments objected that claims that breast implants have no effect on the nursing of infants are unsubstantiated.

FDA agrees that interference with breast feeding of infants is a potential risk to health presented by this device because the implants may reduce the ability of breast feeding women to deliver an adequate quantity of milk. Although most augmentation patients are of childbearing age, there are no data on this potential risk. FDA believes that PMA's or PDP's for the silicone inflatable breast prosthesis should contain information on the effect of the device on the breast feeding of infants.

L. Benefits of the Device

18. One comment stated that a positive psychological benefit for the silicone inflatable breast prosthesis should be assumed. Other comments maintained that the published studies have already established that breast prostheses provide a positive psychological benefit.

The agency believes that the potential psychological benefits offered by the device are an important part of the device's efficacy. Consequently, FDA believes the psychological benefit of the silicone inflatable breast prosthesis should be demonstrated in clinical trials and reported in a PMA or PDP application.

19. Seven comments stated that the determination of psychological benefit is problematic for several reasons: (1) There are no validated standardized psychological tests for measuring psychological benefit; (2) existing tests for psychological well-being and self-esteem are confounded by multiple life variables, including the patient's general health, sexual functioning, and understanding of the potential complications when making the decision to have a silicone inflatable breast prosthesis implanted; and (3) there is a lack of suitable controls for both reconstruction and augmentation patients. One comment suggested that benefit be assessed with ''quality of life'' questionnaires, using patients as their own controls and assessing a wide range of variables. Another comment stated that it would be ''unduly burdensome and needlessly distressful'' to subject women requesting breast implants to psychological assessment testing.

Among the seven comments there was general agreement that patients should be followed for a long period of time after the surgery, perhaps even 10 to 15 years. This is complicated because, during this period, other issues related to self-esteem and a feeling of well-being may confound the determination of psychological benefit. Some comments stated that the assessment of psychological benefit should be different for reconstruction and augmentation patients.

FDA agrees that designing studies to assess the psychological benefit of implantation with a silicone inflatable breast prosthesis may be difficult. In the 1995 guidance document, FDA suggested that the effectiveness of the device can be measured by assessing: (1) The degree of maintenance (if applicable) or of enhancement of a woman's psychological well-being postimplantation, and (2) the anatomical effect provided by the device. FDA added that both assessments should be balanced against any illness or injury associated with the use of the device. FDA further stated that the level of benefit derived from the device may depend on whether the device is used for augmentation mammoplasty, correction of congenital or traumatic breast anomalies, or reconstruction mammoplasty after tumor removal, and recommended that benefit data be stratified by these categories of use. 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 § 860.7(c)(2).

M. Need for Risk Benefit Information

20. Three comments agreed that risk/benefit data should be collected, but questioned the need to include such data in a PMA.

FDA believes that it is appropriate for PMA's or PDP's to contain risk/benefit data to enable the agency to determine whether there is reasonable assurance of the safety and effectiveness of the silicone inflatable breast prosthesis.

N. PMA Contents

21. 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 silicone inflatable breast prosthesis, as well as several general comments on the appropriate contents of a PMA.

FDA believes that the points raised in these comments are addressed in great detail in the 1995 draft guidance. The guidance addresses all types of data, including manufacturing, preclinical, and clinical, expected to be submitted. Additionally, manufacturers already have begun submitting manufacturing and preclinical data to the agency in preparation for the call for PMA's or PDP's.

III. Findings With Respect to Risks and Benefits

A. Degree of Risk

1. Fibrous Capsular Contracture

Contracture, the formation of a constricting fibrous layer around the silicone inflatable breast prosthesis, is a risk associated with both augmentation and reconstruction mammoplasty. Contracture may result in excessive breast firmness, discomfort, pain, disfigurement, displacement of the implant, and psychological trauma. Procedures, including corrective surgery or surgical removal of the device and adjacent tissue, may be required to relieve the symptoms associated with contracture. The effects of contracture can vary from a reduced satisfaction with the device to causing a woman to seek explantation of the device. Although severe cases are rare, less severe contracture is the most common adverse event associated with the silicone inflatable breast prosthesis.

2. Deflation

The deflation of a silicone inflatable breast prosthesis is the loss of saline volume from the device as a result of rupture, valve failure, or a defect in the device. Deflation is not life-threatening, but the loss of saline destroys the shape of the implant, and surgery may be required to remove and replace it. Because of the need for an additional surgery, deflation is a serious adverse event. Deflation incidence data, as a function of time after implantation, are not currently available.

3. Infection

Infection is a risk associated with any surgical implant procedure, including implantation of the silicone inflatable breast prosthesis. Compromised device sterility and surgical techniques may be major contributing factors to this risk. Skin and bacteremic flora may also have a role in infection in the periprosthetic area. Infection may increase fibrous capsular contracture and result in a need for removal of the device.

4. Interference With Early Tumor Detection

The presence of a silicone inflatable breast prosthesis may interfere with standard mammography procedures by producing a shadow that obscures visualization, or by reducing contrast by compressing overlying breast tissue. Mammography of the augmented breast requires special techniques and skills and may result in increased exposure to radiation.

5. Human Carcinogenicity

The potential for developing cancer as a result of the long-term implantation of silicone inflatable breast prostheses cannot be eliminated as a potential risk associated with the silicone inflatable breast prosthesis.

6. Human Teratogenicity

Although FDA is not aware of data indicating that the silicone inflatable breast prosthesis is associated with teratogenic and reproductive 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. Reproductive effects are particularly important because many augmentation patients are of childbearing age.

7. Adverse Immunological Effects and/or Connective Tissue Disorders

The potential for developing immunological effects and/or connective tissue disorders as a result of long-term exposure to the silicone inflatable breast prosthesis remains uncertain. Since the publication of the proposed rule 5 years ago, new epidemiological data (Refs. 1 and 2) addressing the relationship between the device 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, or of an atypical, as yet undefined, syndrome or disease, cannot be eliminated based on these data.

8. Calcification

Calcification of the fibrous capsule surrounding the silicone inflatable breast prosthesis involves the deposition of mineral salts in the capsule. Neither the incidence nor the risk to health of calcification are established.

9. Biological Effects of Silica

Amorphous fumed silica is bound to the silicone in the elastomeric shell of the silicone inflatable breast prosthesis. Silica presents a potential risk which should be addressed in a PMA or PDP.

B. Benefits of the Device

The silicone inflatable breast prosthesis is intended to reconstruct or augment the female breast. Reconstruction or augmentation surgery is elective in nature, although implantation of a silicone inflatable breast prosthesis is often an integral part of the reconstructive patient's total treatment.

Although a definitive psychological study to assess the benefits of the silicone inflatable breast prosthesis may be difficult to conduct, FDA believes data are needed to document whether the device is effective for its intended use.

IV. Final Rule

Under section 515(b)(3) of the act, FDA is adopting the findings as published in the preamble to the proposed rule and is issuing this final rule to require premarket approval of the generic type of device, the silicone inflatable breast prosthesis, by revising § 878.3530(c).

Under the final rule, a PMA or a notice of completion of a PDP is required to be filed on or before November 17, 1999, for any silicone inflatable breast prosthesis 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 November 17, 1999. 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 silicone inflatable breast prosthesis 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 November 17, 1999, 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 silicone inflatable breast prosthesis 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 , 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 silicone inflatable breast prosthesis. Further, FDA concludes that investigational silicone inflatable breast prostheses 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 silicone inflatable breast prosthesis. For any silicone inflatable breast prosthesis 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 silicone inflatable breast prosthesis 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 Enforcement 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.

If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. FDA expects that up to seven manufacturers will submit a PMA or PDP for the silicone inflatable breast prosthesis. FDA estimates that it costs up to $1 million to submit a PMA or PDP. As noted previously, the silicone inflatable breast prosthesis was classified into class III on June 24, 1988, and FDA published a proposed rule to require a PMA or PDP for this device on January 8, 1993. Thus, manufacturers have long been aware of the need to develop information in support of a PMA or a PDP. Moreover, since the publication of the proposed rule, FDA has been working closely with manufacturers to assist them in preparing for the submission of a PMA or a PDP. 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 § 878.3530(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 office above between 9 a.m. and 4 p.m., Monday through Friday.

1. 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.

2. 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.

3. Institute of Medicine, ''Safety of Silicone Breast Implants,'' National Academy Press, Washington, DC, 1999.

List of Subjects in 21 CFR Part 878

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 878 is amended as follows:

PART 878—GENERAL AND PLASTIC SURGERY DEVICES

1. The authority citation for 21 CFR part 878 continues to read as follows:

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

2. Section 878.3530 is amended by revising paragraph (c) to read as follows:

§ 878.3530 Silicone inflatable breast prosthesis.

* * * * *

(c) *Date PMA or notice of completion of a 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 November 17, 1999, for any silicone inflatable breast prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before November 17, 1999, been found to be substantially equivalent to a silicone inflatable breast prosthesis that was in commercial distribution before May 28, 1976. Any other silicone inflatable breast prosthesis shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.

Dated: March 29, 1999.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning and Legislation.

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