ADDRESSES: The hearing will be held at the Quality Hotel Capitol Hill, 415 New Jersey Ave. NW., Washington, DC. Written comments may be submitted to HQUSACE, ATTN: CECW–OR, Washington, DC, 20314–1000.

FOR FURTHER INFORMATION CONTACT: Mr. Ed Bonner or Mr. Sam Collinson, Regulatory Branch, Office of the Chief of Engineers, at (202) 272–0199.

SUPPLEMENTARY INFORMATION: The hearing will be held in accordance with the Corps public hearing regulations at 33 CFR part 327. The hearing will be transcribed. Persons desiring to testify at the hearing are requested to limit their statements to 15 minutes. Filing of a written statement at the time of giving the oral statement would be helpful and facilitate the job of the court reporter. Persons wishing to speak at the hearing need only fill out a card that will be available at the entrance to the hearing room. Advance requests to speak may be mailed to the Office of the Chief of Engineers at the address given above.

Dated: March 15, 1991.

Steve Matteson,

Colonel, Corps of Engineers, Assistant Chief, Construction and Readiness Division, Directorate of Civil Works.

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Part V

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 878

General and Plastic Surgery Devices; Effective Date of Requirement for Premarket Approval of Silicone Gel-Filled Breast Prosthesis; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 878

[Docket No. 88N-0244]

General and Plastic Surgery Devices; Effective Date of Requirement for Premarket Approval of Silicone Gel-Filled 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) for the implanted silicone gel-filled breast prosthesis, a generic type of medical device intended to augment or reconstruct the size and/or contour of the female breast. Commercial distribution of this device must cease, unless a manufacturer or importer has filed with FDA a PMA for its version of the implanted silicone gel-filled 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 for preamendments devices. (See section 513(d) (3) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c(d)(3).) The agency identified the silicone gel-filled breast prosthesis as one of the high-priority devices that would be subject to PMA requirements (January 6, 1989; 54 FR 550 at 551). This rulemaking is consistent with FDA's stated priorities and Congress' requirement that class III devices are to be regulated by FDA's premarket approval review. This action is being taken under the Medical Device Amendments of 1976 (Pub. L. 94-295). The preamble to this rule responds to comments received on the proposal to require the filing of a PMA.

EFFECTIVE DATE: April 10, 1991.

FOR FURTHER INFORMATION CONTACT: Kenneth A. Palmer, Center for Devices and Radiological Health (HFZ-410), Food and Drug Administration, 1390 Piccard Dr., Rockville, MD 20850, 301-427-1090.

SUPPLEMENTARY INFORMATION:

I. Introduction

This regulation is final upon publication and requires PMA's for all silicone gel-filled breast prostheses classified under 21 CFR 878.3540 and all devices that are substantially equivalent to them. PMA's 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)).)

In the **Federal Register** of June 24, 1988 (53 FR 23874), FDA published a final rule (21 CFR 878.3540) classifying into class III (premarket approval) the silicone gel-filled breast prosthesis, a medical device. Section 878.3540 (21 CFR 878.3540) of FDA's regulations setting forth the classification of the silicone gel-filled breast prosthesis intended for medical use applies to: (1) Any silicone gel-filled 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 gel-filled breast prosthesis in commercial distribution before May 28, 1976.

In the **Federal Register** of May 17, 1990 (55 FR 20568), FDA published a proposed rule to require the filing, under section 515(b) of the act (21 U.S.C. 360e(b)), of PMA's for the classified silicone gel-filled breast prosthesis and all substantially equivalent devices. In accordance with section 515(b)(2)(A) of the act, FDA included in the preamble to the proposal 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 (55 FR 20568 at 20570).

The preamble to the proposal also provided an opportunity for interested persons to submit comments on the proposed rule and the agency's proposed findings, and, under section 515(b)(2)(B) of the act, provided the 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 gel-filled breast prosthesis was required to be submitted by June 1, 1990. The comment period initially closed on July 16, 1990. Because of several requests, FDA extended the comment period for 60 days to September 14, 1990, to ensure adequate time for preparation and submission of comments (55 FR 29223).

FDA did not receive any petitions requesting a change in the classification of the silicone gel-filled breast prosthesis. The agency did receive a total of 2,670 comments in response to the proposal of May 17, 1990. This total number represents comments from individuals, manufacturers, professional societies, consumer and health groups, and attorneys. The comments primarily addressed issues relating to the significant risks associated with the use of silicone gel-filled breast prostheses. Many comments were made by patients who had received breast reconstruction or augmentation and indicated favorable experience with this device. Several comments described adverse effects associated with the devices, largely reflecting the profile of the risks identified in the proposal.

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

A. General Comments

1. A few comments disputed the accuracy of the device description for breast prostheses. These comments are summarized as follows:

(a) The device description is incorrect in that the devices classified by FDA were not intended to be filled by the surgeon with silicone gel;

(b) The device description of the shell is incorrect in that the devices classified by FDA do not contain stabilizers in the shell;

(c) The device description of the silicone gel is incorrect in that the devices classified by FDA do not contain stabilizers or fillers in the gel; and

(d) The term prosthesis, as used in the classification definition, is incorrect in that it applies to an implant.

FDA disagrees with the comments. The device classification description, including characteristics referenced in these comments, was prepared to describe the composition of silicone gel-filled breast prostheses that were in commercial distribution before enactment of the Medical Device Amendments. This classification description represented FDA's understanding of the preamendments device, and was proposed as the device description in the **Federal Register** of January 19, 1982 (47 FR 2820).

In response to FDA's proposed classification of the device, no comments were submitted that disputed FDA's characterization and description of the preamendments device, except as discussed in section II A, comment 2. During the classification process FDA received no comments regarding those aspects of the identification of this device now highlighted in comments to FDA's section 515(b) proposed rule. The proposed device classification description was slightly altered after a review of the comments and finalized in the **Federal Register** of June 24, 1988 (53 FR 23874).

While devices marketed today may not be identical to the classification definition, they, nevertheless, have been found to be substantially equivalent to

the classified preamendments device and, thus, are subject to this final rule. Importantly, there has never been confusion regarding FDA's intent to regulate as class III devices silicone gel-filled breast prostheses notwithstanding compositional differences. FDA disagrees with the fourth comment regarding its improper use of the word "prosthesis." Contrary to the comment's contention, the term prosthesis appropriately describes either internally or externally used devices.

2. One comment asked that the double lumen silicone gel-filled breast prosthesis be deleted from any final call for PMA's for silicone gel-filled breast prostheses until FDA publishes a classification proposal for the specific device type. The comment stated that the double lumen prosthesis was not subject to the 1982 proposed regulations (47 FR 2815), nor was it the subject of a separately published classification proposal. Therefore, the comment concluded that the device was not classified pursuant to a duly promulgated regulation subject to the notice-and-comment rulemaking procedures of the Administrative Procedure Act (APA).

FDA disagrees with this comment. In 47 FR 2815, FDA proposed not to classify the double lumen silicone gel-filled/saline breast prosthesis. At that time FDA believed that the double lumen device did not belong in the classification proposed for the silicone gel-filled breast prosthesis and, therefore, proposed to exclude it. A comment was received challenging FDA's position and contending that the double lumen device did, in fact, belong under the proposed classification (see 53 FR 23863). FDA reexamined the available information and requested information from manufacturers. After review of all available information, FDA determined that the proposal not to classify the double lumen device was in error. FDA agreed with the comment and classified the double lumen device after clarifying the identification of the generic type of device. The classification of the double lumen prosthesis was final in 1988. The comment did not challenge that classification upon which the present rulemaking, in part, relies. Even assuming the correctness of the comment, nevertheless, the comment could not now attempt to void this section 515(b) rulemaking with a late challenge to a prior proceeding.

3. One comment stated that Congress never intended "old" (preamendments) devices to be subjected to the same scrutiny as "new" devices. The comment stated that Congress intended that less rigorous scientific evidence should be applied to "old" devices. The comment further stated that FDA should accept meaningful scientific data from the 20 years of use of the device rather than require prospective clinical studies of these devices.

FDA does not believe that Congress intended to differentiate between "old" and "new" devices with respect to the requirement that valid scientific evidence was needed to support a PMA approval. Neither section 513(a)(3) nor 515(d) of the act makes any distinction between "old" and "new" devices with regard to the requirements for approval. However, FDA does expect that more retrospective data, which, by its historical character, is generally less detailed and rigorous than prospectively gathered data, would be available for use in supporting the approval of "old" as opposed to "new" devices. FDA states that scientific evidence, including retrospectively gathered data, is acceptable to support a PMA approval, as long as the data are valid scientific evidence within the meaning of 21 CFR 860.7(c)(2).

4. Two comments stated that the proposed rule does not document or support the type or degree of risks to be reduced or eliminated by the PMA requirement.

FDA disagrees that the proposal has not documented and identified risks associated with these devices and the degree of these risks to be eliminated or reduced by the premarket approval process. The purpose of a PMA is to identify for each specific device the amount of risk and benefit present. Based on the identification of such risks and benefits, and considering specific labeling for a device related to its use and risks, the agency may then determine whether an acceptable showing is made to allow the device to remain on the market.

5. One comment stated that requiring data for the risks, such as connective tissue disease, tuberculosis, chronic infections, tuberculin positivity, and immunological disease, that were not identified in the final classification regulation, without first establishing the need and appropriateness for such data in an open public session before an FDA advisory panel, would place manufacturers at a disadvantage in complying with the agency's request for PMA's.

FDA disagrees with this comment. Findings, or the lack thereof, in the classification regulation do not control the legality of this proceeding. Section 515(b) of the act (21 U.S.C. 360e(b)) sets forth what must be contained in the notice of a proposed regulation requiring PMA's, and the identification of risks and benefits are required parts of the notice. (See section 515(b)(2)(A)(ii) of the act (21 U.S.C. 360e(b)(2)(A)(ii)).) Moreover, FDA's listing of risks and benefits does not eliminate or reduce a PMA applicant's obligation of identifying and quantifying all risks associated with the use of its device known to that applicant.

6. One comment stated that there is a concern about statements in the proposal that would preclude the use of data gathered on these devices since their final classification in 1988. Further, it stated that information gathered on devices with 20 years of experience should not be excluded from PMA's.

FDA is not aware of any such statements or attempts to exclude certain data. Any data that constitute valid scientific evidence and show the safety and effectiveness of a device are acceptable in a PMA.

7. One comment stated that FDA should define how data contained in a premarket notification submission (510(k) submission) submitted under section 510(k) of the act (21 U.S.C. 360(k)) should be used to support PMA's for silicone gel-filled breast prostheses, and that FDA should clarify why 510(k) data are not sufficient for use in addressing FDA concerns.

FDA disagrees and notes that PMA content requirements are contained in section 515(c) of the act and part 814 (21 CFR part 814) of FDA's regulations. Moreover, any data that constitute valid scientific evidence, whether present in a 510(k) submission or available from any other source, may be used to support a PMA.

8. Several comments stated that sufficient thought and time had not been given to define what tests are necessary to ensure that all the various device designs are safe and effective. The comments stated that the proposed rule does not provide specific justification and guidance for the testing required. The comments requested a reopening of the 515(b) process and a postponement of the final 515(b) notice until after specific guidance on device testing is agreed upon by FDA and the manufacturer. The comments went on to say that, after tests are agreed upon, adequate time must then be provided to allow manufacturers to conduct those required tests.

FDA disagrees with these comments. Section 515(b) does not require FDA to provide guidance for tests for PMA's prior to issuing a call for PMA's. While FDA discussed numerous tests that suggest the content of a PMA for a

silicone gel-filled breast prosthesis, these tests were suggestive and not intended to bind a PMA applicant to any specific study or set of studies.

The preamble to the notice contained a statement of what FDA believes are the risks to health posed by a silicone gel-filled breast prosthesis. The identification of risks and benefits of the device was supplied consistent with the act and suggest the areas requiring documentation and study for those preparing PMA's for these devices. The proposed rule, or any part thereof, was not intended as FDA's statement of required content of PMA's for silicone gel-filled breast prostheses. Section 515(c) of the act identifies the required content of any PMA. FDA believes that the requirements stated in the act can be met by several means. FDA is prepared to accept any and all valid scientific evidence in its evaluation of the safety and effectiveness of these devices.

Eight years have passed since these devices were first proposed for class III and more than 30 months have elapsed since these devices were placed in class III by final regulation. FDA believes that manufacturers have had notice, consistent with Congress' intent, to gather the information necessary to provide a reasonable assurance of the safety and effectiveness of these devices. It is not responsible to suggest that Congress intended manufacturers to sit tight and not develop PMA's until a 515(b) regulation became final. Indeed, the act specifically requires submissions 30 months after the final classification of a preamendments device or within 90 days of a final 515(b) regulation, whichever is later. (See section 501(f)(2)(B) of the act (21 U.S.C. 351(f)(2)(B)).) Congress intended that manufacturers anticipate a final 515(b) regulation and be prepared to make appropriate applications or discontinue distribution of their devices. Id.

9. One comment stated that FDA has utilized old, unrelated anecdotal evidence or unsupported opinion without supplying a rationale or reasoning in identifying risks associated with silicone gel-filled breast prostheses. The comment went on to state that FDA has misread, misquoted, acted in a biased and unreasoning manner, and utilized information not appearing in the administrative record, thus acting arbitrarily and capriciously. The comment requested that FDA reevaluate all the literature and reassess the degree of risk prior to issuing a final 515(b) regulation.

FDA disagrees with these comments. The classification process for this device was conducted in accordance with section 513 of the act, and a class III designation was determined appropriate for the device. The notice for this rulemaking sets forth the elements required by section 515(b) of the act. The history of the classification of these devices and the proposed notice contain documentation which supports FDA's regulatory action. The records of these processes show that FDA has not acted in an arbitrary or capricious manner. FDA's review of the record shows that it has reasonably identified the risks to health associated with the silicone gel-filled breast prosthesis. By requiring PMA's for these devices at this time, FDA is not ignoring the clinical history of silicone gel-filled breast prostheses. FDA, based on the record in this proceeding, is exercising its discretion to determine that now is the time to require PMA's for silicone gel-filled breast prostheses. An unchallenged class III designation means that these devices are to be subject to PMA's, and this rule accomplishes Congress' mandated goal.

10. Several comments stated that the incidence of fibrous capsular contracture (contracture), gel migration, teratogenicity, autoimmune disease, and calcification is highly variable and not well established. The comments stated that these events are difficult to estimate because of numerous factors including: the lack of well designed studies; insufficient, unstated or varying follow-up periods; different manufacturers of the devices; lack of information on the number and types of devices implanted; and varying medications and surgical methods used. Some of the comments also stated that existing studies are more descriptive than analytical, control groups are difficult to design and recruit, and populations are too small to establish an association between silicone gel-filled breast prostheses and teratogenicity and calcification.

FDA agrees with these comments. However, sufficient literature identifies these risks associated with the device. It is the purpose of obtaining PMA's for the device to determine whether a risk/benefit assessment justifies the continuation of the distribution of any specific breast prosthesis.

11. Several comments stated that the incidence of contracture, implant rupture and gel leakage has declined over the years. Various comments attributed the decline in contracture to submuscular implantation, the introduction of polyurethane coating, the use of texturized surfaces on implants, improvements in surgical technique and the use of postoperative exercises. Several comments stated that voluntary improvements in the design and materials of silicone gel-filled breast prostheses have reduced the incidence of rupture and leakage.

FDA acknowledges that the design of silicone gel-filled breast prostheses and surgical technique have evolved over time. FDA believes that neither the literature nor other data currently available to FDA definitively describe differences in the incidence of problems attributable to device design and/or variations in surgical procedures. Sufficient information exists identifying contracture, rupture, and leakage as risks to health associated with the silicone gel-filled breast prosthesis. It is the purpose of PMA's to determine whether these risks can be controlled to provide reasonable assurance of the safety and effectiveness of these devices for their intended use. Even a decline in the incidence of risks would not be a reason to abandon the regulation to require PMA's for silicone gel-filled breast prostheses.

12. Several comments stated that PMA requirements for contracture, infection, and other adverse effects should be limited to an analysis of the literature and other available data, labeling and patient education materials that analyze and report the available data, and a plan for postmarket review of the incidence of the risks to health.

FDA disagrees with these comments. FDA believes that literature and other available information are potential sources of the data for PMA's. To the extent that existing data are sufficient to support an approval of a PMA, FDA is comfortable with approving an application consisting of such data; however, this response should not be construed as suggesting that FDA is aware of publicly available information that would support a PMA approval. FDA disagrees that a postmarket surveillance plan alone, or in conjunction with the above, will be sufficient to support PMA approval.

13. Many comments stated that certain references cited in the proposed rule failed to demonstrate a causal relationship or a strong association between the implantation of a breast prosthesis and the onset of risks such as gel bleed, gel migration, calcification, delayed detection of breast tumors, carcinogenicity, teratogenicity and autoimmune diseases or connective tissue disorders.

FDA agrees that the references cited do not establish or refute the existence of a causal relationship between silicone gel-filled breast prostheses and these risks. However, the literature cited by FDA provides evidence that these potential risks are associated with the use of the device and are not trivial.

Investigation of these risks, in the context of a PMA, is reasonable.

14. Several comments stated that certain specific references cited in the proposed rule (55 FR 20568) by FDA did not support the identification of gel bleed (Refs. 25, 31, 32, 36, 42, 53, and 57), interference with tumor detection (Refs. 44 and 48), carcinogenicity (Refs. 30, 38, 50 through 52, 54, 56 through 59, 61 through 68, 77 through 83, 85, 86, 97, 99, and 121 through 123), autoimmune diseases and immunological disorders (Ref. 96), calcification (Refs. 24, 93 through 95, and 99) and contracture (Refs. 5, 7, 8, 13, 19, 26, and 31) as risks to health. One comment stated that some references (Refs. 7, 97, 98, and 101) did not support the device description contained in the proposal.

FDA agrees in part and disagrees in part with these comments. FDA acknowledges that the following references were inappropriately cited: For gel bleed, Refs. 25, 31, 36, 42, 53, and 57; for interference with tumor detection, Ref. 48; for carcinogenicity, Refs. 30, 38, 50, 54, 57 through 59, 65 through 67, 86, and 121 through 123; for autoimmune diseases and immunological disorder, Ref. 96; for calcification, Refs. 24, 94, 95, and 99; and for contracture, Refs. 5, 26, and 31. FDA agrees that Refs. 97 and 98 do not support the device description as stated in the proposal. FDA disagrees that the following references were incorrectly cited: for gel bleed, Ref. 32; for interference with tumor detection, Ref. 44; for carcinogenicity, Refs. 51, 52, 56, 61 through 64, 68, 77 through 83, 85, 97, 99; for calcification, Ref. 93; and for contracture, Refs. 7, 8, 13, and 19. With regard to the references supporting the device description, FDA believes that Refs. 7 and 101 contain documentation for the stated device description. FDA notes that the following references, which were not challenged by the comments, also support the noted risks to health: For gel bleed, Refs. 7, 9, 20, 24, 27 through 29, 33 through 35, 37, 69, 118, and 120; for interference with tumor detection, Refs. 45, 47, and 49; for carcinogenicity, Refs. 53, 69, and 102; for autoimmune diseases and immunological disorders, Refs. 39 through 41; for calcification, Refs. 18, 100, and 125; and for contracture, Refs. 1 through 4, 6, 9 through 12, and 14 through 18.

15. Several comments stated that other silicone containing medical devices produce migratory silicone droplets or particles and that the public is exposed to silicone through many environmental sources. One comment stated that, because of this more general exposure to and absorption of silicone, biologic risks from gel migration attributable to breast prostheses are doubtful and that studies of the anatomic distribution of silicone gel from the device would, therefore, be wasteful and not illuminating. One comment stated that FDA has treated the degree of risk and benefit in a disparate manner compared with other silicone implants.

FDA agrees that individuals are environmentally exposed to silicone polymers from other medical devices and other sources. No evidence was provided by the comments, and FDA is not aware of evidence, that environmental exposures to silicone would mask the effect of a ruptured silicone gel-filled breast prosthesis. The amount of silicone material available for release into a patient from a silicone gel-filled breast prosthesis is considerably larger than that available from other devices, or for that matter, in FDA's opinion, from other sources. When one device poses risks different from another, even if both are made from similar or even identical materials, the level of regulatory control must change. Although humans are exposed to various silicone compounds from a variety of environmental sources, most of these compounds, while containing silicone molecules, are compounds distinct from the silicone polymers used in breast prostheses. FDA believes that identification of all systemic biologic effects of silicone gel from breast prostheses must be part of the determination of safety and effectiveness, which can be achieved, in part, by the examination of the anatomic distribution of migrating silicone polymers.

16. Many comments stated that FDA overstated the risks to health of the silicone gel-filled breast prosthesis and understated the benefits from breast augmentation and reconstruction.

FDA disagrees with these comments. FDA acknowledges that the proposal did not contain a detailed examination of all components and aspects of the benefits of breast augmentation and reconstruction. Although two comments provided detailed identification of benefits of breast augmentation and reconstruction, these two comments did not identify any category of benefit not already identified by FDA in the notice. FDA disagrees that the notice overstates the risks from the device. The notice only identified the risks to health, and information is needed to fully characterize the significance of the risks to health. FDA believes that, without more detailed information, it is impossible to determine whether or not the risks identified in the notice are overstated or understated, particularly when considered in the context of the device's benefits, for any specific silicone gel-filled breast prosthesis.

17. Several comments stated that the risks to health of carcinogenicity, teratogenicity, infection, and interference with tumor detection, and the overall risk/benefit analysis, should be addressed by epidemiological or historical cohort studies and not require prospective studies prior to PMA approval. Some of these comments went on to state that valid scientific evidence sufficient to permit a valid risk/benefit analysis already exists and that FDA should accept this information in PMA's.

FDA agrees that epidemiological or historical cohort studies could serve as a source of the valid scientific evidence necessary to support the approval of a PMA. FDA believes that PMA applications are necessary to provide the valid scientific evidence needed for a risk/benefit analysis.

18. One comment urged FDA to finalize the proposed regulation for silicone gel-filled breast prostheses. It stated that manufacturers have been on notice for 2 years that they would have to provide data showing the safety and effectiveness of these devices, and it recommended that the final premarket approval regulation be published immediately, thereby triggering manufacturers' obligations to submit PMA's.

FDA agrees that the filing of a PMA for the silicone gel-filled breast prosthesis should be required by finalizing the 515(b) regulation. FDA is promulgating this final rule to require a PMA for the device within 90 days of publication, consistent with the act.

B. Fibrous Capsular Contracture

Numerous comments stated that: no single factor has been demonstrated to be the sole cause of contracture; the etiology of contracture is unknown; the etiology may not be identified by present scientific methodology or by prospective clinical trials; and unidentified host factors may play a role. One comment stated that FDA has offered no discussion of the possible causes of contracture.

FDA agrees that the etiology of contracture is unknown and that as yet unidentified host factors may play a role. Nonetheless, contracture is the most commonly documented risk associated with the silicone gel-filled breast prosthesis, and clinical data in the form of valid scientific evidence can show the rate of contracture for any specific silicone gel-filled breast

prosthesis. With this information, the agency can make a risk/benefit assessment of the various devices.

One comment stated that the Baker grade IV contracture is the only grade that can be considered to represent a health risk, while another comment remarked that contracture seldom presents a health problem. A third comment added that, when contracture occurs, it can be treated appropriately with no detriment to the patient's health.

FDA believes that, whenever a contracture is characterized by excessive breast firmness, discomfort, pain or disfigurement, it represents a potential health risk and may require corrective procedures, including surgery.

C. Gel Migration

Several comments noted that the agency made no attempt to distinguish between migration of silicone gel released by rupture or released by bleed. FDA agrees with the comments but notes that such a distinction is not necessary to the extent that rupture or gel bleed results in the migration of silicone gel.

Two comments stated that silicone lymphadenopathy and granuloma are rare occurrences and of questionable clinical significance. FDA disagrees that, although rare, silicone lymphadenopathy and granuloma formation are of questionable clinical significance. The agency cited evidence of silicone lymphadenopathy and granuloma formation to demonstrate that migration of both liquid silicone and silicone gel takes place and that silicone polymer materials are capable of producing adverse effects at sites distant from the implantation or injection site. The scientific evaluation of these risks for a specific device will permit a full risk assessment for a judgment of whether a specific device should remain in commercial distribution.

D. Infection

Many comments stated that, according to studies cited by the comments, infection occurs in a very small percentage of patients and the risk of infection is the same as or less than that of other procedures.

FDA disagrees that infection is an insignificant risk associated with silicone gel-filled breast prostheses. The proposed rule cites the occurrence of this complication as a potentially serious adverse effect. Data are needed to quantify the incidence of infection.

E. Tumor Detection

Several comments recognized that the presence of silicone gel-filled breast prostheses may complicate the interpretation of mammographic images. A few comments from women with implants argued that the presence of implants may facilitate the detection of lesions.

FDA agrees that the presence of an implant may compromise the interpretation of a mammographic procedure. FDA is unable to agree that the implant facilitates the detection of lesions, because the comments did not support their claims with scientific literature, and FDA is unaware of any literature supporting this position. FDA notes that the level of diagnostic assurance provided by modified mammographic procedure(s) has not been established. FDA believes that, in order to provide reasonable assurance of the safety and effectiveness of these silicone gel-filled prostheses, results from well-controlled studies must be properly analyzed and presented to evaluate the risk and/or benefit for early tumor detection posed by the device.

F. Degradation of Polyurethane Foam-Covered Prostheses

Several comments stated that the polyurethane foam material on silicone gel-filled breast prostheses degrades over time with a potential breakdown product of 2,4-diaminotoluene (TDA), a known carcinogen in animals. One comment suggested that the Delaney clause of the act required the agency to remove any device which contains a known carcinogen, such as TDA, from the market.

FDA agrees that the polyurethane foam used as a coating for silicone gel-filled breast prostheses can degrade to form TDA and that this represents a potentially serious risk of the device. FDA disagrees that the Delaney clause applies to medical devices.

G. Human Carcinogenicity

Numerous comments were received on the subject of the carcinogenicity of silicone. The comments make the following contentions: human case reports which described pathogenesis due to fluid silicone are not relevant because the silicone was not of medical grade; the possibility of chemical induction of sarcomas in animals was inappropriately inferred; coincidental occurrence of malignant carcinomas and breast prostheses does not establish a linkage; and animal studies are irrelevant because the observed sarcomas are solely due to physical (solid state) carcinogenesis and such risks are not applicable to humans. One comment stated that valid studies have established that breast implants do not cause cancer in humans.

FDA disagrees with these comments. Carcinogenesis is a putative risk secondary to implantation of any material. After review of all available information, the agency continues to believe that carcinogenicity is a potential risk that must be assessed in a PMA.

H. Human Teratogenicity

One comment stated that the requirement for teratology testing would be satisfied by a single generation rat reproductive toxicity study while a second comment preferred a rabbit study.

FDA believes that information in the form of well-designed, single generation animal studies would be appropriate. Additionally, a PMA applicant may choose to submit appropriate human studies, or properly gathered and analyzed historical data, to establish the teratogenic potential of a silicone gel-filled breast prosthesis.

I. Autoimmune Disease

Several comments stated that the number of reported cases of scleroderma or other connective tissue disorders or diseases of the immune system among implanted women does not exceed the incidence of these diseases in the general population.

FDA believes that, presently, it is not clear whether the incidence of these diseases in implanted women is the same as or greater than the incidence in the general population. The uncertainty surrounding this risk requires that it be investigated. FDA may not ignore a risk because evidence identifying it is not definitive. Indeed, to do so would not be sound public health management.

Two comments stated that "human adjuvant disease" should be abandoned as a risk of a breast implant because this disease appears to be highly specific to rats, with a few isolated cases in mice, following the injection of Freund's Complete Adjuvant. There is no evidence that this disease occurs in humans. Further, the comments stated that a consensus statement from the American Medical Association on this issue concludes that this designation is inappropriate.

FDA agrees with these comments.

J. Calcification

Several comments stated that the etiology of calcification is unknown. Other comments stated that it is impossible to determine whether calcification is due to the implant or other factors, such as postoperative

infection, a metabolic disorder, trauma, or other circumstances. Comments also stated that calcification is unlikely to be confused with a malignancy when appropriate mammographic views are taken.

FDA agrees that the etiology of calcification is unknown. Moreover, no valid scientific data have been submitted demonstrating that calcification will not mask interpretation of mammographic films, or contribute to diagnostic error. Calcification, therefore, remains a risk associated with breast implants that should be addressed in a PMA.

K. Benefits and Risks of the Device

1. Benefits

Over 2,600 comments were received that described the psychological and psychobiological benefits of breast prostheses. FDA agrees with those comments that recognized psychological and psychobiological benefits from these devices. However, FDA believes that the degree of benefit offered by this device must be carefully and accurately defined by analysis of all relevant data. The proposed rule identified some of the benefits found in the scientific literature and also identified some areas where FDA believes that more data are needed to provide reasonable assurance that the device is safe and effective for its intended use. FDA received approximately 2,600 comments from women who are satisfied with their breast augmentation or reconstructive surgery. The comments stated that it is important that women be given the chance to freely choose silicone gel-filled breast implants as an option as long as they are well informed of the benefits and risks of the surgery.

FDA agrees with these comments as to potential benefits and agrees that women should be able to choose whether to use any silicone breast implant that is ultimately approved for marketing by FDA. As noted above, FDA is aware of potential benefits derived from silicone gel-filled breast prostheses.

One comment stated that extensive available data and information indicate that, with appropriate safeguards including complete and informative labeling, silicone gel-filled breast prostheses used for both reconstruction and augmentation have a favorable "risk/benefit profile," and that a significant segment of the population benefits from the availability of both silicone covered and polyurethane covered, silicone gel-filled breast prostheses. A second comment stated that significant patient experience and success support a favorable "risk/benefit ratio."

FDA agrees that silicone gel-filled breast prostheses offer benefits to a segment of the population. FDA disagrees that the available data are adequate to provide a complete and accurate risk/benefit analysis.

Several comments stated that surgeons recognize a successful clinical experience with their patients who received silicone gel-filled breast prostheses.

FDA agrees that a large proportion of practicing surgeons find that the implantation of the silicone gel-filled breast prostheses in their patients is successful.

Although FDA nowhere suggests that the requirement of a PMA pursuant to a section 515(b) rulemaking identifies the need to explant a silicone gel-filled breast prosthesis, several women have telephoned the agency with this concern. The rulemaking reflects the agency's exercise of its discretion to now require PMA's and does not concern individual medical determinations, including the need to explant the device. Moreover, the rulemaking is not intended to pass judgment over the safety and effectiveness of any specific device. The purpose of the rulemaking is to require information upon which FDA may rely to make a safety and effectiveness determination.

2. Risks

Several comments stated that the risks from silicone gel-filled breast prostheses fall into two categories: (1) short-term risks, e.g., those related to the surgical procedure, infection, device failure, contracture and interference with tumor detection; and (2) long-term risks, e.g., carcinogenesis, teratogenicity and autoimmune disease.

FDA agrees that the risks of any implant fall into the broad categories of short-term and long-term risks. FDA disagrees that the risks of infection, device failure, contracture and interference with tumor detection are exclusively short-term risks. FDA believes that these risks are both short and long-term in nature.

A comment stated that a breast reconstruction patient can generally accept a procedure with greater inherent long-term risks than can a candidate for augmentation. The comment went on to say that the level of short-term risk to be tolerated by both reconstruction and augmentation patients should be the same and that short-term risks generally do not affect short-term health but, the ability to derive benefit from the implantation of a silicone gel-filled breast prosthesis.

FDA believes that the risk/benefit analyses for breast reconstruction and augmentation patients differ. However, FDA does not believe, in the absence of complete data on the extent, nature, and degree of the device's risks and benefits, one can state that reconstruction patients can accept greater long-term risks than augmentation patients. FDA agrees that the short-term risks to health for both categories of breast prosthesis patients appear generally to be the same.

A comment stated that there are many factors contributing to complications which are outside the control of manufacturers.

FDA agrees with this comment. FDA believes that requiring PMA's for the device will provide data identifying those risks that can be controlled by manufacturers and those risks that are controlled by the implanting surgeons or the patient. FDA believes that, once all risks are properly characterized, proper labeling and disclosures to physicians and patients will contribute to a reasonable assurance of the safety and effectiveness of any silicone gel-filled breast prosthesis included within the device classification and ultimately approved by FDA.

One comment asked if any quantitative long-term risk information was uncovered by the review of all existing national and international registries of breast prostheses that was recommended by FDA's advisory panel. Quantitative long-term risk information was not uncovered in the review. (See Transcript of General and Plastic Surgery Devices panel meeting, January 26, 1989.)

L. PMA Data Requirements

A major contention of comments received by FDA was that adequate guidance on the content of a PMA for a silicone gel-filled breast prosthesis was not provided. The agency considered the comments and concluded that its suggestions for PMA content in the notice are useful [1] with the exception of

[1] Other information that applicants may utilize in preparing their PMA's is available in various Federal Register notices (47 FR 2810, 53 FR 23856 and 55 FR 20568) and in the transcripts of General and Plastic Surgery Devices Panel meetings (September 9, 1982, January 28 and 27, 1983, November 22, 1988, and January 26, 1989). Additionally, manufacturers have in the past met with the agency to discuss PMA's and that opportunity is still available. The agency emphasizes that its suggestions regarding PMA content are no more than suggestions and that manufacturers carry the burden of complying with the content requirements of the section 515(c) of the act and FDA's regulations (21 CFR 814.20).

changes noted in the following paragraphs:

1. Several comments suggested that preclinical and clinical testing to detect autoimmune disease and immunological sensitization should be deleted.

FDA agrees that preclinical autoimmune disease or immunological sensitization testing may not be necessary. The agency believes that pre- and postimplantation measurements of circulating antibodies, as well as clinical followup of immunological adverse effects, such as autoimmune disease or connective tissue disorders, could address these immunological issues.

2. Several comments suggested that tensile strength and ultimate elongation testing should be added to the testing requirements and shear strength and viscosity testing deleted.

FDA agrees with these comments.

3. Several comments addressed the issue of steroid absorption to the breast prosthesis. One comment requested clarification of the term "steroid adsorption" and inquired if this was to mean adsorption to the envelope elastomer or absorption into the silicone gel. FDA notes that the term should be "steroid absorption" and refers to absorption into the silicone gel of the prosthesis.

Other comments questioned the basis for investigating steroid absorption. The comments noted that the labeling contraindicates the use of steroids with breast implants, and a literature search failed to identify any significant absorption of steroid hormones by silicone gel-filled breast prostheses. Another comment stated that the potential toxicological effects of steroid absorption should be investigated in appropriate preclinical studies.

FDA agrees that the potential toxicological effects of steroid absorption by silicone gel-filled breast prostheses should be investigated in appropriate preclinical studies. The literature cited in the proposed rule (55 FR 20588, Ref. 84) indicates that preferential absorption of systemic steroids could cause a local or systemic hormone imbalance with unknown toxicological effects.

4. Several comments argued that testing of the silica was unnecessary because amorphous (fumed) silica is bound to the silicone, and therefore not independently reactive. The comments further stated that, even if silica was not bound, but free to react, it would not be fibrogenic in the same way as crystalline silica.

FDA does not believe that there is sufficient information available to conclude that amorphous silica does not produce the same kind of biological effects as crystalline silica. Therefore, FDA believes that data demonstrating the safety of amorphous (fumed) silica should be submitted in PMA's.

FDA has reexamined its proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the silicone gel-filled breast prosthesis to meet the statute's approval requirements. The agency concludes that its proposed findings and its conclusion discussed in the preamble to the proposed rule are appropriate. Accordingly, FDA is promulgating this final rule requiring premarket approval for the silicone gel-filled breast prosthesis under section 515(b) (3) of the act and is summarizing its findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the silicone gel-filled breast prosthesis to have an approved PMA, and with respect to the benefits to the public from the use of the device.

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 prosthesis, is a risk associated with both augmentation and reconstruction. 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.

2. Silicone Gel Leakage and Migration

Silicone gel leakage and subsequent migration from the silicone gel-filled breast prosthesis may occur as a result of rupture of the envelope or gel "bleed" through the envelope and represents a risk associated with the use of this device. Migration of the gel into the human body presents the potential for development of adverse effects such as granulomas or lymphadenopathy. Rupture of the silicone gel-filled breast prosthesis necessitates surgical removal and possible replacement of the device.

3. Infection

Infection is a risk associated with any surgical implant procedure including silicone gel-filled breast prostheses. Various device surface characteristics may potentiate infection. Also, compromised device sterility and surgical techniques may be major contributing factors to this risk. Endogenous flora may also have a role in infection in the periprosthetic area.

4. Interference With Early Tumor Detection

The presence of a silicone gel-filled breast prosthesis may interfere with the standard mammography procedures used to screen patients for breast cancer because the prosthesis may produce a shadow on the radiograph that obscures visualization of a significant portion of the breast. In addition, the implant compresses overlying breast tissue, reducing contrast and thereby making mammographic assessment more difficult. Mammography of the augmented breast requires special techniques and skills and may result in increased exposure to radiation. Even under the best of circumstances, silicone gel-filled breast prostheses are likely to limit the effectiveness of the examination for breast cancer detection.

5. Degradation of Polyurethane Foam Covered Breast Prostheses

The polyurethane foam material used to cover silicone gel-filled prostheses is known to degrade over time with a potential breakdown product of TDA, a known carcinogen in animals. Difficulty with the removal of this type of prosthesis may occur. If explantation becomes necessary, surgical removal of the implant may include adjacent tissue due to tissue ingrowth into the foam. Fragmentation and disappearance of the foam may occur.

6. Human Carcinogenicity

The potential for developing cancer as a result of long-term implantation of silicone gel-filled breast prostheses remains a potential risk associated with these devices.

7. Human Teratogenicity

Teratogenesis includes the origin or mode of production of a malformed fetus and the disturbed growth processes involved in the production of the malformed fetus. The risk of teratogenicity in association with prolonged gel migration from a silicone gel-filled breast prosthesis remains a potential risk.

8. Autoimmune Disease and Immunological Sensitization

Immunological sensitization may be a serious risk associated with the implantation of silicone gel-filled breast prostheses. Questions have been raised about the relationship between silicone and various connective tissue disorders, including scleroderma.

9. Calcification

Calcification of the fibrous capsule surrounding the implant may compromise interpretation of mammographic films and may contribute to diagnostic errors or delays in diagnosis of cancerous lesions.

In order to establish conditions for use that will eliminate or minimize these risks and determine whether the risks of using the device are balanced by benefits to patients, FDA concludes that silicone gel-filled breast prostheses should undergo premarket approval. The premarket approval process will reasonably assure a safe and effective device by assessing the safety and effectiveness of each silicone gel-filled breast prosthesis and determining labeling that is necessary to reduce risks associated with the device.

B. Benefits of the Device

Silicone gel-filled breast prostheses are intended to reconstruct or augment the female breast. Reconstruction or augmentation surgery is elective in nature although it may be considered therapeutic in the sense that it is considered part of the patient's total treatment. The large volume of comments that FDA received from women implanted with the device identify the psychological benefits of implantation as substantial. Nonetheless, these benefits still require careful documentation. Although a definitive study to determine the psychological benefits of the silicone gel-filled breast prosthesis may be difficult to conduct, nevertheless, FDA believes that protocols can and should be developed that provide data to quantify the benefits of this device. In addition, objective data are needed to document whether the device is effective for its intended use, i.e., the augmentation or reconstruction of the size and/or contour of the breast.

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 gel-filled breast prosthesis, by revising paragraph (c) of § 878.3540.

Under the final rule, a PMA is required to be filed with FDA within 90 days of the effective date of this regulation for any silicone gel-filled 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 the 90th day past the effective date of this regulation. An approved PMA is required to be in effect for any such device on or before 180 days after FDA files the application. Any other silicone gel-filled breast prosthesis that was not in commercial distribution before May 28, 1976 or that has not on or before 90 days after the effective date of this regulation been found by FDA to be substantially equivalent to a silicone gel-filled breast prosthesis that was in commercial distribution before May 28, 1976, is required to have an approved PMA in effect before it may be marketed.

If a PMA for a silicone gel-filled 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 (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 (21 CFR Part 812) are met.

Under § 812.2(d) of the IDE regulations, FDA hereby stipulates that the exemptions from the IDE requirements in § 812.2(c) (1) and (c)(2) will no longer apply to clinical investigations of the silicone gel-filled breast prosthesis. Further, FDA concludes that investigational silicone gel-filled breast prostheses are significant risk devices as defined in § 812.3(m) and advises that as of the effective date of § 878.3540(c) the requirements of the IDE regulations regarding significant risk devices will apply to any clinical investigation of a silicone gel-filled breast prosthesis. For any silicone gel-filled breast prosthesis that is not subject to a timely filed PMA, 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 for investigational purposes must cease. FDA advises all persons presently sponsoring a clinical investigation involving the silicone gel-filled 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 25.24 (a)(8) and (e)(4) 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. Economic Impact

FDA has examined the economic consequences of this final rule in accordance with the criteria in section 1(b) of Executive Order 12291 and found that the rule will not be a major rule as specified in the Order. The agency believes that 21 firms will be affected by this rule. Therefore, the agency certifies under the Regulatory Flexibility Act (Pub. L. 96–354) that the rule will not have a significant economic impact on a substantial number of small entities. An assessment of the economic impact of this final rule has been placed on file in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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

2. Section 878.3540 is amended by revising paragraph (c) to read as follows:

§ 878.3540 Silicone gel-filled breast prosthesis.

* * * * *

(c) *Date premarket approval application (PMA) is required.* A PMA is required to be filed with the Food and Drug Administration on or before July 9, 1991 for any silicone gel-filled breast prosthesis that was in commercial distribution before May 28, 1976, or that has on or before July 9, 1991 been found to be substantially equivalent to a silicone gel-filled breast prosthesis that was in commercial distribution before May 28, 1976. Any other silicone gel-filled breast prosthesis shall have an approved PMA in effect before being placed in commercial distribution.

Dated: March 11, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 91–8408 Filed 4–9–91; 8:45 am]

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federal register

Wednesday
April 10, 1991

Part VI

The President

Executive Order 12758—Addition to Level IV of the Executive Schedule

Part IV

The President

Federal Register
Vol. 56, No. 69
Wednesday, April 10, 1991

Presidential Documents

Title 3—

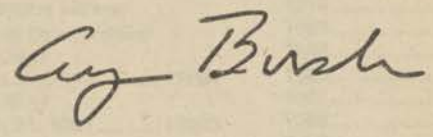
The President

Executive Order 12758 of April 5, 1991

Addition to Level IV of the Executive Schedule

By the authority vested in me as President by the Constitution and laws of the United States of America, including section 5317 of title 5 of the United States Code, and in order to place an additional position in Level IV of the Executive Schedule, it is hereby ordered that section 1–101 of Executive Order No. 12154, as amended, is further amended by adding the following new subsection:

"(j) Director of the National Institutes of Health."



THE WHITE HOUSE,
April 5, 1991.

[FR Doc. 91–8657
Filed 4–9–91; 11:14 am]
Billing code 3195–01–M