Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA

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This document supersedes "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated August 13, 2001.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Plastic and Reconstructive Surgery Devices Branch
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to Docket Number: 99D-4003 and the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance document, contact Ms. Samie Allen at (301) 594-3090 or email sxn@cdrh.fda.gov.

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This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

1. Introduction

This guidance document provides industry with updated information from that described in "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated August 13, 2001. The update is based on FDA's review of additional breast implant applications and discussions with industry. The primary differences between this version of the guidance document and the August 2001 version, other than reformatting the guidance, are the addition of the ***Device Description*** section and updated suggestions on information to provide to FDA in the ***Mechanical Data, Clinical Data***, ***Clinical Data Presentation***, and ***Labeling*** sections.

This guidance document is intended to provide important device description, preclinical, clinical, and labeling information that should be presented in a premarket approval (PMA) or a product development protocol (PDP) application. This guidance document may also be useful in the preparation of an investigational device exemption (IDE), a reclassification petition, or a master access file (MAF). The information discussed pertains to breast implants filled with saline, silicone gel, and alternative filler intended for breast augmentation, breast reconstruction, and revision. However, this guidance document does not address tissue expanders, which are unclassified devices for temporary use.

This guidance document serves as a supplement to other FDA publications on PMA, PDP, and IDE applications and should not be construed as a replacement for these documents. For general PMA information, refer to 21 CFR 814 or to the Premarket Approval Manual, available at http://www.fda.gov/cdrh/manual/pmamanul.pdf. For specific input regarding PDP applications, refer to "**The Guidance for Industry: Contents of a Product Development Protocol**," available at http://www.fda.gov/cdrh/pdp/pdpguide.pdf. For general IDE information, refer to 21 CFR 812 or to the Investigational Device Exemptions Manual, available at http://www.fda.gov/cdrh/manual/idemanul.html.

Although use of this guidance document to prepare preclinical and clinical protocols will not ensure PMA, PDP, or IDE approval, following this guidance document should reduce unnecessary work by you and should allow for a more efficient review by FDA.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance document, we

carefully considered the relevant statutory criteria for FDA decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance document and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. Background

There are three types of breast implants, all of which may be intended for breast augmentation, breast reconstruction, and revision.

2.1 Saline-Filled Breast Implant

A saline-filled breast implant has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, which is inflated to the desired size with sterile isotonic saline. Saline-filled breast implants may vary in shell surface, shape, profile, volume, and shell thickness. Most have valves that self-seal and a patch that covers the manufacturing port. The sterile saline used as a filler material should conform to United States Pharmacopeia (USP) standards of Normal Physiological Saline (injection grade) which has a concentration of 0.15M and a pH of 7.2-7.4.

There are three types of saline-filled breast implants. Type one is a fixed volume implant with a single lumen that is intraoperatively filled with the entire volume of saline via a valve. Type two is an adjustable volume implant with a single lumen that is intraoperatively filled with saline via a valve and has the potential for further postoperative adjustment of the saline. Type three is a prefilled saline implant.

In the *FEDERAL REGISTER* of June 24, 1988 (53 FR 23856), FDA issued a final ruling classifying the silicone inflatable (saline-filled) breast prosthesis into Class III (21 CFR 878.3530). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require premarket approval. On January 8, 1993 (58 FR 3436), FDA issued a proposed rule requiring a PMA. On August 19, 1999 (64 FR 45155), FDA required a PMA or PDP for these devices to be filed with the Agency within 90 days. To date, an approved PMA or PDP is required for marketing.

2.2 Silicone Gel-Filled Breast Implant

A silicone gel-filled breast implant has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, which is filled with a fixed amount of silicone gel. Silicone gel-filled breast implants may vary in shell surface, shape, profile, volume, and shell thickness. Most have a patch that covers the manufacturing port.

There are three types of silicone gel-filled breast implants. Type one is a fixed volume implant with a single lumen containing a fixed amount of silicone gel. Type two is an inflatable double lumen implant with the inner lumen containing a fixed amount of silicone gel and the outer lumen designed with a valve for filling with saline intraoperatively. Type

three is an inflatable double lumen implant with the outer lumen containing a fixed amount of silicone gel and the inner lumen designed with a valve for filling with saline intraoperatively, with the potential for postoperative adjustment.

In the *FEDERAL REGISTER* of June 24, 1988 (53 FR 23863), FDA issued a final rule classifying the silicone gel-filled breast prosthesis into class III (21 CFR 878.3540). On January 6, 1989 (54 FR 550), FDA published a notice of intent to require premarket approval. On April 10, 1991 (56 FR 14620), FDA required a PMA for these devices be filed with the Agency within 90 days. To date, an approved PMA or PDP is required for marketing.

2.3 Alternative Breast Implant

An alternative breast implant typically has a silicone rubber shell with a filler other than saline or silicone gel. The filler material may or may not be a gel. However, an alternative breast implant may also have an alternative shell other than that made from silicone rubber. You should keep in mind that the additional information other than that described below may be necessary for alternative shell breast implants.

All alternative breast implants are class III post-amendment devices that require an approved PMA or PDP for marketing.

3. Device Description

The Background section above (Section 2) provides a very basic device description for each of the three types of breast implants. This section provides the type of device description information to include in your submission. However, depending on the particular design of your implant, additional information may be necessary.

You should provide the following device description information:

- a written description of each component that comprises the implant (e.g., shell, gel, patch, textured surface, valve)
- the specific materials (with suppliers) for each component
- a description of any connector systems, fill tubes, and injection domes, including materials
- magnified sketches of the implants, depicting the placement/use of the connector systems, fill tubes, and injection domes
- a description of when the implant is filled by the surgeon if not a prefilled implant (i.e., intraoperatively and/or postoperatively)
- a description of any overexpansion/overfill of the filler material, even if on a temporary basis
- a description of the method by which the implant is sterilized
- the following summary table of all implants under review (example of information included):

Style	Shell Surface	Shape / Profile	Volume (cc)	Width (cm)	Height (cm)	Projection (cm)	Minimum Shell Thickness
XXXX	Smooth	Round, High	125-650	9-16	8.4-15	3.1-5.7	0.015”

Depending on the design features of the implant, you may need to expand the table above. For example, if there is overexpansion of the implant, you should include a column related to this information.

4. Chemistry Data

4.1 General Information

You should provide the following general information regarding the chemicals/materials used in the manufacture of your breast implant:

- the common names and trade names of each chemical/material (including additives, plasticizers, and antioxidants)
- the specific role of each chemical/material in the manufacturing process and/or in the final device
- the location of the material within the device (e.g., shell, filler, valve, adhesive)
- the chemical name, the mean molecular weight, and a measure of the polydispersity for each polymeric component
- material safety data sheets for each chemical
- MAF numbers for each material, including specific volume and page number references.

You should provide confirmation that the silica used in the elastomer shell dispersion is in the amorphous form, rather than crystalline form.

Sections 4.2 through 4.5 describe chemical analyses of the elastomer shell, including the patch and valve. Sections 4.6 through 4.9 describe chemical analyses of the filler material. Changes in design features, such as texturing, variations of device components, such as patches or valves, or changes in sterilization may necessitate additional analyses.

4.2 Extent of Crosslinking

The manufacture of the shell involves curing of polymeric components of silicones by chemical crosslinking. You should provide the extent of crosslinking from at least three different lots to confirm the uniformity of the degree of crosslinking across lots. Suggested methods to determine the degree of crosslinking include:

- measurement of Young’s modulus at low strain (this is approximately proportional to crosslink density)
- measurement of equilibrium swelling of the polymeric component by a good

solvent

- determination of the amount of unreacted crosslinker from the total extractables
- any other acceptable scientific method.

You should also perform a Fourier Transform Infrared Spectroscopy (FTIR) analysis on the cured polymer to confirm the presence of silicone functional groups.

4.3 Extractables

An analysis of the extractable or releasable chemicals is necessary to identify potentially toxic chemicals and estimate the upper limits of the chemicals that could be released to the patient. The following is one suggested method to obtain extractable data. You should perform the extraction of the shell for chemical analyses with at least one polar solvent (i.e., ethanol or a mixture of ethanol-water) and two non-polar solvents (i.e., dichloromethane and hexane) at 37°C. To determine the duration of the exhaustive extractions, you should conduct a series of successive extractions by exposing the sample to the solvent for a period of time, analyzing the solvent for extractables, replacing with fresh solvent, exposing the sample again for a period of time, analyzing, and repeating the process. When the level of the analyte for the extraction is one-tenth (0.1) the level in the previous extraction, the extraction is deemed complete so that a 10% correction to the total extractable material can be applied. In cases where this condition may not occur because of extremely slow migration of the higher molecular weight material, apply the test to the contents of the extract with molecular weights of ≤1500 Daltons because these are the compounds of greatest interest. Add all separate analyte levels to calculate the cumulative value and, via the sample/solvent ratio, the sample and device levels. You should use the total extraction from the polar solvent and the extraction from one of the non-polar solvents that yields the higher amounts of extractables for both quantitative and qualitative analyses. For extracts that may contain oligomeric or polymeric species, you should provide the molecular weight distribution, along with the number and weight average molecular weights and the polydispersity. You should perform an FTIR analysis on the extractable residuals.

You should provide the following data from the extractables:

- identification and quantification of all compounds below a molecular weight of ≤1500 Daltons after exhaustive extraction of the final sterilized shell. These include, but are not limited to:
  - residual monomers, cyclic and linear oligo-siloxanes
  - known toxic residues such as polychlorinated biphenyls (PCBs) if peroxide curing process is involved
  - aromatic amines if polyurethanes are used
- the percent recovery, especially for the polydimethylsiloxanes (up to D20)
- evidence that shows that exhaustive extraction has been achieved with one of the solvents

- identification of all experimental methodology[1] and provide raw data (including instrument reports) with all chromatograms, spectrograms, etc. You should also provide the practical quantitative limit when the analyte of interest is not detected.[2]

4.4 Volatiles

You should analyze the elastomer shell for volatile components suing a headspace detector.

4.5 Heavy Metals

You should provide qualitative and quantitative analyses for heavy metals on the final finished shell. The heavy metal analyses should include, but not be limited to, analyses of the following metals: platinum (Pt); tin (Sn); zinc (Zn); chromium (Cr); arsenic (As); lead (Pb); antimony (Sb); nickel (Ni); and copper (Cu). In addition, for the metal used as the catalyst in the curing reaction, you should provide the valence state and the amount of residue of the catalyst.

In lieu of providing a complete heavy metal analysis on the finished shell, you may provide the purity of the catalyst (with trace elements) used in the raw shell material, along with an analysis of the finished shell for just the catalyst metal used.

4.6 Saline Filler

Normal physiological sterile saline has a long history of use in breast implants and is standardized by the USP. As stated above, the sterile saline used with your implant should conform to USP standards of Normal Physiological Saline (injection grade) which has a concentration of 0.15M and a pH of 7.2-7.4. If your breast implant is used with any other saline, provide a complete chemical analysis of that saline.

4.7 Silicone Gel Filler

The analyses of the silicone gel are very similar to those for the elastomer shell. You should provide the following information on the final sterilized gel:

- qualitative and quantitative analyses for extractables (such as cyclic polysiloxanes), including:
  - characterization of the polymers present
  - molecular weight averages and polydispersities of the polymers
  - identification and quantification of all compounds present with a molecular weight of ≤1500 Daltons
- qualitative and quantitative analyses for volatiles
- qualitative and quantitative analyses for heavy metal contents
- all physical properties of the gel, including viscosity, cohesivity, and approximate

[1] For example: Gel Permeable Chromatography (GPC), Gas Liquid Chromatography (GLC), Mass Spectometry (MS), Atomic Emission Detector (AED), and FTIR.
[2] Keith, L. Compilation of EPA's Sampling and Analysis Methods. Lewis publishers, 1992.

crosslink density (if possible)

- the percentage of silicone oil and its chemical and physical properties (e.g., molecular weight, viscosity).

4.8 Alternative Filler - Polymer

You should provide the following information on a final sterilized polymer filler:

- the rationale for the use of the specific alternative filler material
- a list of all the components used in the synthesis and the method of synthesis of any polymer used in the preparation of filler (if it is a synthetic polymer) or the source and isolation procedure of the polymer, if it is a natural polymer
- quantitative analyses of monomers (if synthetic polymer) and their safety profile
- the method of purification of the polymer
- complete physical and chemical characteristics of the polymer (e.g., viscosity, molecular weight)
- the formulation of the polymer (the ratio of polymer should be specified if the filler material is a mixture of more than one component)
- the structural analyses of the polymer, including molecular weight distribution
- quantification and identification of all chemicals below a molecular weight of 1500 Daltons, including the monomer and their characterization
- the trace metal/heavy metal analysis and the valence state if metals were used as catalysts in the polymerization reaction
- the crosslink density (if it is a synthetic and cured material).

4.9 Alternative Filler – Non-Polymer

You should provide the following information on a final sterilized non-polymer filler:

- the rationale for the use of the specific alternative filler material
- composition of the non-polymer, including characterization of smaller-molecular weight components
- the method of purification of the non-polymer
- complete physical and chemical characteristics of the non-polymer (e.g., viscosity, molecular weight)
- the source and isolation procedure of the non-polymer
- the structural analyses of the non-polymer, including molecular weight distribution.

5. Toxicology Data

5.1 General Information

A toxicological assessment is necessary because breast implants contain not only the major polymeric materials (e.g., polymerized polydimethylsiloxane) but also low molecular weight components, such as monomers, oligomers, catalysts, and residues from the manufacturing or sterilization processes that can leach out into the patient's body. The toxicological safety assessment is based on information from:

- the chemical composition of the device
- the pharmacokinetic analysis
- the standard battery of toxicological tests.

The chemical composition provides a list of the chemicals present. The pharmacokinetic analysis determines the rates of absorption, distribution, metabolism and elimination of the substances absorbed into the patient's body. The standard toxicological testing battery is used to detect unidentified toxins and to quantify the exposure to known toxic compounds.

5.2 Pharmacokinetic Studies

Knowledge of the pharmacokinetic behavior of potentially toxic chemicals provides a scientific assessment of the potential of the chemicals to accumulate at concentrations that cause human health risks. The pharmacokinetic study design you choose should be based on the information needed to address the worst case assumption (i.e., that all of the material in the implant is absorbed into the body at once). If this assumption, with the addition of safety factors, results in toxic levels of exposure, demonstrations of slow diffusion of substances from the implant into the body or rapid metabolism or excretion of the substances by the patient may negate the worst case assumption. The pharmacokinetic testing of toxins of concern should determine the rates of absorption into and clearance from the blood, the distribution in the body, and the rates of metabolism and/or excretion. If radiolabeling is used, the device should be labeled in ways that will reflect the fates of all of the components of interest. For additional information, see ISO/FDIA 10993-16.

5.3 Toxicological Testing

You should perform the standard battery of toxicological tests separately on both the final sterilized shell and filler. These tests include:

- cytotoxicity
- short and intermediate-term implantation tests
- acute systemic toxicity
- hemocompatibility
- immunotoxicity
- reproductive toxicity
- teratogenicity
- genotoxicity
- carcinogenicity (including subchronic and chronic toxicity testing).

Refer to ISO-10993 "Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing" and the FDA-modified guidance document "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing," available at http://www.fda.gov/cdrh/g951.html, for more details about the toxicological tests above.

Refer to Section 5.4 below for special considerations regarding the toxicological tests.

5.4 Special Considerations

You should assess the level of immunotoxicity of the shell and any leachable compounds from the shell and the gel. For more information, you should refer to the CDRH "**Immunotoxicity Testing Guidance,**" available at http://www.fda.gov/cdrh/ost/ostggp/immunotox.pdf.

Reproductive and teratogenicity studies should measure the rates of conception, as well as the numbers of fetal deaths and malformations. The studies should include at least two generations. You should test individual compounds at the highest possible exposure that does not produce non-reproductive systemic toxicity.

Genotoxicity and carcinogenicity information addresses the potential to cause cancer, which may arise from leachable compounds and/or from degradation products of the device. The short-term genotoxicity testing should, at minimum, consist of bacterial mutagenicity (including point mutations and frameshift mutations), the mouse lymphoma test as a mammalian forward mutation assay, and an in vivo rodent micronucleus test. If these tests are negative, and the device is made from dimethylsiloxane polymers only, the 2-year carcinogenicity test will not be required unless other safety issues arise.

If carcinogenicity testing is required, you may combine the carcinogenicity study with the subchronic and chronic toxicity testing by removing animals from the carcinogenicity study at appropriate intervals. The carcinogenicity study needs to be initiated with additional animals to compensate for the animals scheduled to be removed. If, however, a subchronic or chronic toxicity emerges during the study, this may interfere with the ongoing carcinogenicity study. Subchronic and chronic toxicity testing are essential because the leaching process may be slow, even when the material is in pulverized form, exposing the animals or cells to very small quantities of the leachable toxicants or carcinogens. Implanted material may also degrade over time, producing toxic degradation products. These toxins might be detected only by subchronic or chronic implantation tests. The subchronic implantation test reports should include gross and histopathology examinations of the tissue surrounding the implanted material and at appropriate sites remote from the implantation site with gross lesions or potential connections to the observed toxicity.

FDA will consider approval of an IDE before the carcinogenicity testing is completed, if the *in vitro* genetic toxicology testing is negative and the clinical carcinogenic experience with the materials continues to support safety.

6. Mechanical Data

6.1 General Information

You should provide individual component and total device testing to evaluate the mechanical properties of your breast implant. These tests are described in Sections 6.2-6.5 below.

You should conduct all testing on finished, sterilized total devices or components (e.g., shell, gel, valve). If the device is sterilized by different methods (e.g., ethylene oxide, gamma radiation), you should perform the testing on samples sterilized by the different methods unless you provide an adequate rationale that the change in sterilization method does not negatively impact the mechanical characteristics.

You should provide complete reports for all testing. Clearly state which implants were tested (e.g., model, size). Provide a description of the test set-up and methods, including sketches or photographs.

FDA believes that you should be able to adequately address material properties, such as tensile strength, ultimate elongation, joint testing, and tear resistance, through your validation and verification manufacturing activities. Therefore, FDA has removed these four material property tests recommended in the August 13, 2001 version of the breast implant guidance document.

6.2 Fatigue Rupture Testing of Total Device

Most materials have a finite fatigue life when repeatedly stressed or flexed. Repeated compression or flexing of the device will, with time, weaken the shell and lead to failure. Therefore, you should perform fatigue compressive testing on the worst case, final, sterilized implant(s) with the thinnest shells allowed by the design release criteria.

Fatigue testing is performed in a constant load or a constant displacement mode. However, you should only perform constant displacement testing if you measure the actual applied loads continuously or at frequent points during the testing and the variation of the actual applied load is minimal. Use the minimal load applied during constant displacement testing to establish the endurance load level.

You should cyclically load the samples to runout or failure at varying loads or displacements to generate an applied force versus number of cycles (AF/N) curve for the worst case implant(s). You should base the runout value on the expected *in vivo* cycles subjected to the implant in its lifetime, and you should provide an adequate rationale for the runout value.

You should test a minimum of three (3) samples at a given load or displacement from static point down to the endurance load level because of the general variance seen in elastomer testing. Start with the static point and keep reducing the load or displacement for each subsequent test until a sample can reach runout without failure. Whether load or displacement control testing is performed, you should provide an AF/N curve for each style tested. These curves may be generated by best-fit approach or by averaging the number of

samples tested to establish a given point. There should be a tight range (e.g., 10%) of points around and at the endurance load level for a cleaner curve.

You should provide the following results for each style tested:

- the resulting endurance load level
- the clinical relevance for the resulting endurance load level, including the incorporation of a safety factor
- the AF/N curve
- the raw data
  - applied loads
  - applied displacements (only for displacement control test)
  - corresponding number of cycles to failure (unless runout reached)
  - sample thicknesses.

6.3 Valve Competence

This testing pertains only to breast implants with valves. Valve competence tests are performed to demonstrate that valve integrity is maintained at *in vivo* loads. Implants can be subjected to hydrostatic forces that tend to force fluid out of the device, causing a deflation and change in size and shape. The most likely source for increased pressure inside the devices would be from patients reclining with various body parts (e.g., head, arm, trunk) pressing on their implants.

ASTM 2051 states that there shall be no leakage observable after a normally closed valve is subjected to a retrograde pressure equivalent to 30cm H_2O for 5 minutes and then to a retrograde pressure equivalent to 3cm H_2O for 5 minutes. FDA does not believe that the load levels described in the ASTM F2051 methodology are clinically relevant; however, this methodology may provide useful information in terms of the valve handling shifts in pressure. Therefore, you should provide a complete report of valve competency testing as per ASTM F2051. You should provide the pass/fail results for leakage.

In addition to the testing above, you should perform destructive testing to address *in vivo* loading conditions. Gradually load the samples until valve failure occurs to define a maximum pressure for the device. You should provide the following results:

- the burst pressures
- the failure modes (including whether the failed test valves reseal upon removal of the excess failure-inducing pressures)
- the clinical rationale for the resulting burst pressures.

6.4 Cohesivity of Silicone Gel or Alternative Filler

You should quantify the cohesivity of a silicone gel or alternative filler. The two methods described in ASTM F703 were not developed to address gels with high cohesivities, such as those currently seen which explains why industry is not obtaining quantifiable results. However, there currently is no other recognized standard for quantifying cohesivity. Also,

there currently is no standard for penetration testing, an indirect measure of cohesivity. Therefore, until a recognized standard is developed to quantify cohesivity, you should provide complete reports of the following tests to address gel cohesivity:

- gel cohesion testing on the final device as described in the cone/pendant method in ASTM F703
- penetration testing on the in-process gel.

For the gel cohesion testing, you should provide the pass/fail results.

For the penetration testing, you should provide a complete description of the penetration test method, the acceptance criteria, and the results.

6.5 Bleed Rates of Silicone Gel or Alternative Filler

Because gel or fluid can bleed through an intact shell, you should provide a complete report of bleed testing to determine the bleed rate of a silicone gel-filled implant or of an alternative filler implant. One possible method is described in ASTM F703. You should provide the following results:

- average weights of gel diffusion per surface area (W_g)
- average weights of gel diffusion per surface area per time interval (R_g)
- sample thicknesses.

7. Other Data

7.1 Stability Data for Alternative Breast Implants

For a breast implant with an alternative polymer or non-polymer filler, you should provide a complete report of long-term stability and accelerated aging testing to demonstrate the effects of time and temperature on the physical properties and chemical composition of the device as a whole and of the filler material. You should measure key physical parameters of the filler, such as viscosity and cohesivity, at each timepoint. If there are mechanical changes, you should conduct complete chemical analyses to explain the physical changes.

7.2 Bleed Material Analysis of Alternative Filler

FDA is concerned with the changes in composition of the alternative filler resulting from long-term chronic bleed, for which there is little known information. Therefore, you should provide a complete report of bleed material analysis of the alternative material that addresses this issue. However, because of the large number of possibilities of components for alternative filler materials, there is no existing test standard. You should provide a complete description of your testing methodology with a rationale. The rationale should be based on the specific chemical make-up of the alternative filler device. FDA recommends submitting a protocol to the review division before initiating this testing.

7.3 Shelf Life Testing

You should provide both real-time mechanical testing and packaging testing to establish the shelf life (i.e., expiration date) for the labeling.

You should perform mechanical testing on representative aged samples at time zero and at various intervals throughout the claimed shelf life. The mechanical tests, at minimum, should include:

- ultimate elongation
- joint
- tensile set
- break force
- valve competency (if applicable)
- gel cohesivity (if applicable).

With regard to packaging testing, you should test the final finished package for initial integrity and maintenance of integrity after selecting the appropriate materials and qualifying the package configuration. You should use test methods that are either validated or standardized.

Initial Integrity

The integrity of the package is tested at time zero. This includes both seal and whole package testing.

The seals of the package are tested for seal integrity and seal strength. Seal integrity may be established by demonstrating that the seal is impermeable and continuous. There are several standardized methods that may be used to determine seal integrity. For example, ASTM F1929 is a dye penetration method for detecting seal leaks. Seal strength should demonstrate that the fiber shedding, splitting, and tearing of the package is within your specifications.

For whole package testing, you may use physical or microbiological test methods. Examples of whole package integrity tests are internal pressure test, dye penetration, gas sensing test, or vacuum leak test. At the present time, there are only a few standardized physical whole package test methods. ASTM D3078 is an example of a test method by bubble emission. Alternatively, you may use the microbial challenge test.

Maintenance of Integrity

The ability of the package to maintain its integrity over time may be evaluated by the same functional tests used for integrity testing. You should expose the package to the environmental stresses imposed by manufacturing, sterilization processes, distribution, handling, vibration, and the storage environment. Stressing should always be performed with the device in the package. You should perform the seal integrity and whole package testing after stressing and at various intervals throughout the claimed shelf life of the package. The data obtained during this time period should remain within the validated limits of the performance specification.

7.4 Retrieval Study

Because the high or unpredictable rate of implant failure and the lack of understanding of the mode of failure are major concerns, FDA believes that a properly structured retrieval study involving clinical observations and laboratory observations/testing may be more useful at this time than pursuing fold flaw and abrasion testing. Information from the retrieval study may lead to changes in manufacturing design specifications, mechanical testing requirements, and/or labeling. The retrieval study involves two portions.

The first portion of the retrieval study involves the collection of data (i.e., clinical observations) at the time of device explantation. The clinical observations should be recorded on a field report form by the surgeon or appropriate healthcare provider at the explant site:

- the reason (i.e., signs and symptoms) for the device explantation
- any complications experienced and the method of resolution
- any action planned (e.g., replacement with another implant with identification of the manufacturer, type, and model of the new device)
- the relevant clinical observations at surgical removal (e.g., appearance of shell for gross defects, the condition of the valves and/or patches)
- whether concomitant capsulectomy is performed
- the presence of discoloration of and quantification of extruded filler
- the presence and extent of implant rupture
- the condition and appearance of surrounding capsule and/or other tissues removed
- the mode of failure of the explant, if known
- the relevant histological examinations of surrounding tissue or cells.

You should implement a standardized method of sterilization for the explant sites to minimize the factors that may impact device mechanical properties.

The second portion of the retrieval study protocol involves the following laboratory observations, testing, and analyses to be completed by you:

- laboratory observations (or device failure characteristics) generally involve visual inspections to note findings such as smooth or sharp crease-edge openings with respect to whether the device was deflated/non-deflated
- material property testing to determine any correlations with reason for explantation
- chemical testing, if necessary
- evaluation, at minimum, of the clinical observations at the time of device explantation removal and your laboratory observations and testing to determine the modes of failure of the explanted devices.

8. Clinical Data

8.1 General Information

FDA believes that a PMA may be filed with a minimum of 2 years of patient follow-up on a sufficient cohort of patients to evaluate the safety and effectiveness of the product. This is based on additional post-PMA filing follow-up for a total of a minimum of 10 years of prospective patient follow-up.

Studies should include the separate patient cohorts of primary augmentation, primary reconstruction, and revision. Because these studies are complicated by the fact that some patients receive implants for different reasons (e.g., a woman may receive one implant for reconstruction and one for augmentation), you should record and analyze the data on both a per patient and a per device basis. You should classify the patient and device by the initial indication at study *entry* according to the following rules:

- If a reconstruction patient undergoes contralateral augmentation, that *patient* is classified as reconstruction. The device classification is one reconstruction and one augmentation.
- If a revision patient (i.e., the patient entered the study due to replacement of an existing implant, regardless of the type or manufacturer of the original implant), undergoes contralateral augmentation, that *patient* is classified as a revision patient. The device classification is one revision and one augmentation.
- If a revision (removal with replacement) occurs during the study (i.e., after initial implantation), the *patient* and *device* is classified based on the indication at original implantation at study entry.

If patients undergo removal and replacement with your implant, then you should continue follow-up. For patients who undergo removal without replacement or removal with replacement with another manufacturer's implant, FDA still encourages you to continue follow-up evaluations**.**

Full patient accounting and adequate and appropriate safety and effectiveness data presentations are essential. **Refer to Section 9 for suggestions for the minimal data presentations that you should provide for breast implants.**

8.2 Clinical Study Design / Statistical Issues

Clinical Study

You should provide a complete description of the clinical study. This includes:

- the study objectives
- the primary and ancillary hypotheses
- the definitions of the study population (i.e., inclusion and exclusion criteria)
- the methods of randomization, if applicable
- the number and locations of investigational sites

- the enrollment procedures
- a description of surgical techniques
- a description of allowable ancillary surgical interventions and/or drugs
- a description of the control group (see paragraph below).

You should provide an explanation of how a concurrent control group was selected, if utilized for comparison. Otherwise, you should provide an adequate justification for lack of use of a concurrent control group and you should utilize historical controls. If you choose to incorporate a concurrent control group, you should select an approved saline-filled breast implant.

Sample Size

You should provide the statistical rationale that the sample size is adequate to provide accurate measures of the safety and effectiveness of the device. This includes, at a minimum:

- identification of effect criteria (i.e., clinically significant difference in the response variables to be detected)
- desired precision for rate estimates (i.e., defined as ½ width of confidence interval)
- statistical error tolerances of alpha and beta
- anticipated variances of response variables (if known)
- any assumptions or statistical formulas with a list of references used
- reasonable estimations of lost-to-follow-up rates
- all calculations used.

You should base sample size estimates on the precision of safety and effectiveness outcomes or detecting a clinically meaningful difference at two years from baseline or from a control group and taking into account the lost-to-follow-up rates estimated for 10 years of patient follow-up. If sample size estimates are based on the precision with which complication rates can be estimated, then the sample size should be large enough to ensure that this precision is within a pre-specified number of percentage points which FDA considers acceptable, based on 95% confidence intervals.

For example, for sufficient numbers of patients with primary augmentation or primary reconstruction (i.e., assuming 75% primary augmentation and 25% primary reconstruction) to determine the rupture rate with reasonable precision, data on 500 patients will be needed at 10 years post-implantation. If you estimate a hypothetical 40% drop out rate at 10 years, then you will need to enroll at least 850 patients to achieve 10-year data on 500 patients. This will provide a worst case precision of +/-4% at a rupture rate of 50%. This precision will improve as the rate moves away from 50%, with a +/-1.9% precision at a rupture rate of 5% or 95%. This pooling of cohorts represents the overall worst case precision. However, FDA recommends that you provide the precisions (i.e., confidence intervals) separately for each patient cohort.

Because both safety and effectiveness data from patients presenting for revision may be significantly different from that of primary implantation patients, you should include a proportion of patients presenting for revision. For example, if you estimate that approximately 20% of patients present for breast implants due to revision, you should increase the final sample size by 20%. Therefore, if you need 850 primary implantation patients, you should enroll approximately 150 revision patients, for a total of 1000 patients.

You should support all marketing claims (both explicit and implied) of equivalence or superiority to existing implants or therapies with statistically justified numbers of patients, clinically relevant endpoints, and direct comparisons made to an appropriate control group.

8.3 Safety Assessment

Complications

The complications below are crucial in determining the risks of breast implants.[3] Therefore, you should collect the following information, regardless of the device relatedness of the event:

- the incidence, timing, and reason(s) for all implant removals, for removal with replacement with your device, for removal with replacement with another manufacturer's device, and for removal without replacement.[4] Reasons for removal may include capsular contracture, rupture/leakage, breast pain, wrinkling, change size/shape, etc.
- the incidence, timing, and reason(s) for any reoperation (additional operation). Reasons for reoperation may include rupture/leakage, wrinkling, ptosis, asymmetry, change size/shape, etc.
- the incidence, timing, and type(s) of additional surgical procedures. Multiple types of surgical procedures may be performed in a given reoperation. Types of additional surgical procedures include capsulotomy, capsulectomy, implant removal with replacement, implant removal without replacement, saline adjustment, reposition implant, drainage of abscess/hematoma/seroma, excision of masses/lymph nodes in ipsilateral axilla or arm of implanted breast, biopsy/cyst removal, etc.
- the incidence, timing, and resolution of all other complications, such as capsular contracture (include Baker Grade), infection, calcification, migration, extrusion, skin erosion, necrosis, lymphadenopathy, delayed wound healing, breast/chest/axillary mass formation, iatrogenic injury, hematoma, pain, seroma, wrinkling, asymmetry, scar formation, visibility of the implant, etc.
- the incidence, timing, and severity of alterations in nipple or breast sensation

[3]Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. {IOM Report}

[4]If a patient undergoes removal and replacement with your implant, then you should continue follow-up on that patient. For a patient who undergoes removal without replacement or removal with replacement with another manufacturer's implant, FDA still encourages you to continue follow-up evaluations on that patient**.**

- the incidence, timing, and severity of interference and/or difficulties with lactation
- the incidence, timing, and nature of difficulties with pregnancy
- the incidence, timing, and cause of patient deaths from post-mortem examinations
- the incidence, timing, and type of new breast cancer diagnosis post-implantation.

FDA recommends that you conduct regularly scheduled evaluations for the occurrence of all complications for a minimum of 10 years post-implantation. Follow-up frequencies are suggested as, at a minimum, 6-10 weeks, 1 year, and then annually thereafter. Annual visits are also recommended to minimize the number of patients lost-to-follow-up.

Connective Tissue Diseases (CTDs)
Despite the large body of information published regarding breast implants and the development of rheumatic or CTD, the association between breast implants and CTD remains unresolved. While recent, large studies[5,6,7] have provided some evidence that breast implants are not associated with a large increase (i.e., relative risk greater than 2) in defined CTD, FDA believes that these data are limited in that they:

- are not prospective (resulting in potential underreporting due to recall bias)
- do not address incomplete symptomatology for definitive diagnosis
- lack consistent evaluations and follow-up
- lack adequate duration of follow-up
- report pooled data from a variety of implant compositions rather than from product specific compositions.

Furthermore, in general, the population for which breast implants is indicated, particularly the augmentation cohort (i.e., females in the reproductive age group), is generally at greater inherent risk for developing CTD than the older population or males.

Therefore, you should collect the following CTD data:

- rheumatic diseases – such as rheumatoid arthritis, systemic lupus erythematosus, discoid lupus, scleroderma, vasculitis, polymyositis, and dermatomyositis
- rheumatic syndromes – such as Raynaud's phenomenon, Sjogren's syndrome, CREST, morphea, carpal tunnel syndrome, multiple sclerosis-like syndrome, multiple myeloma-like syndrome, chronic fatigue syndrome, and fibromyalgia

[5]Hennekens CH, Lee IM, Cook NR, *et al.* Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA*. 1996; 275:616-621.
[6]Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liange MH. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med*. 1995; 332:1666-1670.
[7]Gabriel SE, O'Fallon WM, Kurkland LT, Beard CM, Woods JE, Melton LJ III. Risk of connective-tissue diseases and other disorders after breast implantation. *N Eng J Med*. 1994; 330:1697-1702.

- rheumatic signs and symptoms - such as hair loss, facial rash, photosensitivity, dry eyes, dry mouth, arthralgias, myalgias, difficulty swallowing, morning stiffness >30 minutes, ocular inflammation/retinitis/optic neuritis, muscle weakness, joint swelling for >6 weeks, pleurisy, skin rash, and lymphadenopathy
- other reported signs/symptoms - such as cognitive dysfunction, fatigue, paresthesia, dizziness, abnormal bruising or bleeding, purpura, unexplained fever, urticaria, telangiectasia, and petechiae.

FDA recommends that you conduct CTD evaluations on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. Patients should have follow-up evaluation(s) by a rheumatologist or other appropriate specialist and with collection of serological information (e.g., anti-nuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), immunoglobulin levels, c-reactive protein (CPK), serum protein electrophoresis (SPEP), complement levels), if indicated.

Silent Rupture for Silicone Gel-Filled Breast Implants

Silent rupture is defined as a loss in the integrity of the shell, regardless of whether or not the silicone gel material has been demonstrated to have migrated from the shell. You should determine the incidence, timing, and clinical consequences of silent rupture via prospective, sequential screening of a subgroup of the study population utilizing diagnostic radiographic or other techniques of adequate sensitivity and specificity.

For standard silicone gel-filled implants, FDA recommends magnetic resonance imaging (MRI) as the current method of choice for detecting silent rupture. MRI of the breast should be performed with a dedicated breast coil and preferably in those centers experienced in performing and interpreting this type of examination (i.e., qualified MRI assessor). The qualified MRI assessor should be blinded to the investigator's judgment of a possible rupture (if applicable) and should perform an independent assessment of each MRI and rate the presence or absence of rupture as definitive, suspicious, or none. The final determination should be made by the qualified MRI assessor rather than the investigator.

FDA recommends that the patients in the silent rupture substudy undergo MRI evaluations at 1, 2, 4, 6, 8, and 10 years.

Mammographic Changes and Detection Difficulties

Breast implants are known to alter the appearance and quality of radiographs produced by conventional mammography. For an individual patient undergoing screening mammography, you should collect the incidence, timing, and extent of tissue fibrosis and calcification around the implant and their impact on the correct and timely detection of breast tumors by mammography.

8.4 Effectiveness Assessment

Anatomical Effect

You should assess the anatomical effect of the implant. This may be evaluated by comparing matched analyses of before and after bra and cup sizes, chest circumference, symmetry, and/or other standardized measurements.

Health Related Quality of Life (HRQL)

You should evaluate the HRQL benefits using valid and reliable instruments to assess the beneficial impact of the device. However, to date, there are no HRQL instruments which have been developed and validated in a breast implant population which capture all of the important domains (i.e., physical, social, emotional) as well as the positive and negative aspects of implantation on breast implant recipients. To make claims of improvement in health related quality of life, you should develop and validate such measures for your implants in a breast implant population.

You should include, at minimum, the following health outcome assessments as secondary endpoints of effectiveness:

- a measure of self esteem (i.e., Rosenberg Self Esteem Scale)
- a measure of body image (i.e., Body Esteem Scale)
- a measure of general health related quality of life (i.e., SF-36).

FDA recommends that you collect HRQL data on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. You should describe the timing of administration of these instruments with respect to delayed versus immediate reconstruction in reconstruction patients.

Satisfaction

We also recommend that you assess global patient satisfaction. Your assessment should incorporate the effects of the initial surgical procedure, any adjunctive surgical and medical procedures, any complications, and whether the expected benefits of the procedure and of the implants have been met. We also suggest you collect patient satisfaction data assessing the effects of device removal, regardless of whether the device was replaced.

8.5 Special Considerations

Implant failure is a critical assessment. Therefore, you should advise against closed capsulotomy because it has been shown to potentially result in implant rupture. Additionally, you should advise against the addition of substances into the filler (i.e., betadine, steroids, and antibiotics) other than those recommended because the substance may potentiate and/or accelerate delamination of the shell.

The stage and status of breast cancer can impact future development of cancer. Furthermore, the presence of chemotherapy, radiation, or other cancer treatments can impact the development of local complications with implants. These issues may impact the evaluation of the safety and effectiveness of the device. Therefore, you should collect these data on all reconstruction patients and on augmentation and reconstruction patients who develop breast cancer during the course of the study.

High lost-to-follow-up rates may impact the evaluation of the safety and effectiveness of the device. You should include a comparison of baseline characteristic between those subjects with complete data and those without to ascertain the presence of any non-respondent bias. Also, you are encouraged to offer incentives for patient retention. Otherwise, you should be prepared to contact lost-to-follow-up patients at the end of the study and to demonstrate that the outcomes for these patients are the same as those for the patients who were compliant with follow-up. Failure to do this may delay filing and/or approval of the PMA because additional clinical studies may be needed.

8.6 Special Considerations for Alternative Breast Implants

The minimum period of both premarket and total patient follow-up is determined individually for each alternative breast implant based on chemical, toxicological, mechanical, and clinical properties of the implant. You should provide at least 2 years of premarket data for PMA filing for any implant and possibly longer premarket follow-up depending on the properties of the implant.

Unless an adequate rationale is provided, you should collect silent rupture data for an alternative breast implant. You should include time course evaluations, incidence, and clinical consequences of silent rupture by MRI or some other appropriate imaging method. Any rationale for not collecting silent rupture data on the alternative filler should be based on chemical and/or mechanical properties as compared to saline (rapid leak) and silicone gel (slow leak) fillers.

8.7 Supplemental Information

Certain outcomes may not be fully evaluated through the preclinical and clinical data above. These outcomes include the risks of cancer(s), connective tissue disorders (typical and atypical), reproductive/teratogenic effects, interference of implant on ability of mammography to detect tumors in breast implants, interference with breast feeding, and the later effects on offspring from women with implants.

Therefore, you should provide a thorough search of current and past medical literature on breast implants to address the range of clinical experience with each of these outcomes as they relate to the specific type of implant (i.e., silicone gel-filled, saline-filled, alternative), as well as the criteria and method of selecting the literature.

You should provide copies of the literature references and develop a table that summarizes the information (see example table below). You should provide the numerators and denominators along with the rates.

Outcomes	Literature	Implant Type(s)
Cancer(s)	#patients with outcome / total patients, rate (%) for article 1 #patients with outcome / total patients, rate (%) for article 2	Saline only Saline/silicone gel
Typical CTDs		
Atypical CTDs		
Reproductive Teratogenic Effects		
Other		

[1] citation for literature article #1
[2] citation for literature article #2

In addition, you should perform a thorough literature search for the safety outcomes reported in the prospective clinical study (e.g., rupture, capsular contracture III-IV, infection). You should provide this information in table format, such as that shown above. Additionally, you should provide the criteria and method of selecting the literature.

FDA recognizes that it may be difficult to provide literature information specific to the subject breast implant type. The literature may pool silicone gel-filled and saline-filled breast implant information together. The literature lack any information specific to alternative filled breast implants. However, you should make every attempt to collect information specific to the subject breast implant type. If no device type-specific data are available, you should provide pooled data (e.g., silicone gel and saline data) from the literature. If pooled data are not available, you should provide data on the other type(s) of breast implant(s). For example, if no literature data exists for alternative-filled implants similar to that under review, then you should provide the literature summary for silicone gel and saline-filled implants.

For alternative breast implants in which the alternative material is used in another type of medical device, you should provide a summary of the literature involving clinical experience with that material.

8.8 Postapproval Study Considerations

Patients should be evaluated for a minimum of 10 years, some of which is premarket and some of which is postapproval evaluation. FDA believes that a minimum of 2 years of premarket data is necessary to support a PMA for this device. The clinical sections above describe the type of premarket data that you should collect.

After approval of a PMA, you may be required to continue follow-up of patients out to 10 years through a postapproval study. The study design of the postapproval study should be based on the specifics of the data submitted in the PMA.

However, you should collect the following type of data annually, at minimum, as part of a postapproval study:

- pain
- capsular contracture
- deflation/rupture
- silent rupture, if applicable
- reasons for reoperations
- reasons for removals
- satisfaction.

After approval of a PMA, you may also be required to develop or continue a retrieval study to collect data on explanted devices.

The following risks may not be fully evaluated through the prospective clinical study described above nor from the literature as discussed in Section 8.7 above:

- cancer(s)
- connective tissue disorders
- reproductive/teratogenic (at birth) effects
- later effects (after birth) on offspring from women with implants
- interference with breast feeding
- interference of implant on ability of mammography to detect tumors in breast implants.

If there is insufficient evidence in the medical literature or from experimental animal data to make reasonable judgments on the effect of implant type (i.e., silicone gel-filled, saline-filled, alternative) on the risks above, FDA may require additional postapproval studies to address them.

9. Clinical Data Presentation

9.1 General Information

This section illustrates the types of safety and effectiveness data presentations you should, at a minimum, submit in a breast implant PMA. We encourage you to provide your own data presentations as well as those described below. While most of these presentations apply to all types of breast implants, some data presentations, such as silent rupture information, are applicable to silicone gel-filled but not to .saline-filled implants.

The majority of the data requested below should be reported for the **separate patient cohorts of primary augmentation, primary reconstruction, and revision** (i.e., the patient status/indication at study *entry*). See Section 8.1 above regarding specific patient cohort classification. Furthermore, you should provide the data on both a per patient and per device basis for most of the items below. Lastly, FDA believes it is essential for you to provide all available data, including those data beyond the 2-year timepoint. The specifics are discussed within each section below.

9.2 Patient Accounting Presentation

You should provide the following information regarding patient accounting:

- a complete patient accounting table on a per patient basis for each separate patient cohort (see below for more details)
- the causes for patients lost to follow-up, as well as any measures to minimize such future events
- the causes for patient and physician-initiated discontinuations
- the causes of any deaths, including reports from post-mortem examinations.

Table 1 below is an example table showing cumulative patient accounting. You should report the deaths and removals cumulatively (i.e., continue adding across the timepoints instead of just reporting the number specific to one timepoint). You should include, at minimum, the following information in the patient accounting table:

Table 1 - Cumulative Patient Accounting

	Periop	1 year	2 years, etc.
Theoretically due[1]	100	85	50
Deaths	0	1	1
Patients with all devices removed without replacement	0	2	2
Patients with all devices removed and replaced with other manufacturer's devices	0	1	3
Patients with all devices removed with replaced with your devices	0	4	6
Expected[2]	100	81	44
Actual (Patients with complete follow-up)	100	68	39
Lost-to-follow-up	0	13	5
Percent Follow-up (Actual/Expected)	100/100 (100%)	68/81 (84%)	39/44 (89%)

[1]Patients who would have been examined according to implant date and follow-up schedules.
[2]Patients theoretically due minus deaths and removals without replacement and removals with replacement with different manufacturer's devices.

FDA believes you need to provide a minimum of 80% follow-up at 2 years at the time of PMA filing.

9.3 Demographics and Baseline Characteristics

You should provide the following information regarding patient demographics, as well as patient, device, and surgical baseline characteristics for each separate patient cohort.

Patient Demographics (per patient basis)

- patient age, height, and weight

Patient Baseline Characteristics (per patient basis)

- indication for use (i.e., augmentation vs. reconstruction vs. revision)

Device Baseline Characteristics (per device basis)

- device surface type (i.e., smooth vs. textured)
- device type (i.e., single vs. multi-lumen), if applicable
- device style and/or size, if clinically relevant
- valve type (e.g., leaf, diaphragm), if applicable

Surgical Baseline Characteristics (per device basis)

- surgical incision site (e.g., periareolar, inframammary fold, axillary)
- incision size
- device placement (e.g., retromuscular, subglandular)
- timing of reconstruction (i.e., immediate vs. delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents, if applicable.

9.4 Safety Data Presentation - Complications

Overall Sum of Complications

You should provide the overall sum of all complications on both a per patient and per device basis for each separate patient cohort at each timepoint. You should provide the total number of events categorized as mild, moderate, severe, etc. (if available). If the same event occurred more than once in the same patient or breast, you should count it more than once.

Cumulative Incidence of Complications

You should provide the cumulative incidence of individual complications at each timepoint on both a per patient and per device basis for each separate patient cohort. You should provide the numerator and denominator used. You should describe how these values were obtained. The denominator is the number of patients or devices at that timepoint.

If the same complication is reported in the same patient or breast more than once, it is counted once in the numerator if that same complication never resolved during the entire follow-up period. If a complication occurs in a patient or breast, resolves, and then recurs at a subsequent timepoint in the same patient or breast, it is counted twice in the numerator.

If more than one different or new complication occurs in the same patient/breast cumulatively, it is counted more than once in the numerator and once in the denominator for per patient and per device reporting for the total (overall) data presentation.

Note that each capsular contracture grade is considered a new or different complication and that a new (after implantation) diagnosis of breast cancer is considered a new complication.

Kaplan-Meier Analyses of Complications

You should provide Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on both a per patient and per device basis for each separate patient cohort and for the total population for every complication including, but not limited to, the following:

- removal for any reason regardless of whether the device was replaced
- removal for any reason with replacement with your device

- removal for any reason with replacement with another manufacturer's device
- removal for any reason without replacement
- any reoperation
- capsular contracture grades II, III, and IV separately
- capsular contracture grades III and IV together
- capsular contracture grades II, III, and IV together
- etc.

Refer to ***Complications*** in Section 8.3 for additional information. Kaplan-Meier analyses should be performed for all complications, regardless of the device relatedness of it.

To avoid the problem of competing risks, a patient experiencing a complication should still be a candidate to experience any other potential complication.

Reasons for Implant Removal
You should provide the cumulative reasons for implant removal for each separate patient cohort at each timepoint. The denominator should be the total number of devices removed since the initial implantation to that timepoint. If more than one reason for removal is reported for a given device, then you should determine the primary reason for removal based on a hierarchy, such as:

- rupture/deflation
- capsular contracture
- infection
- necrosis/extrusion
- hematoma/seroma
- wrinkling
- implant malposition
- asymmetry
- breast pain
- scarring
- patient request for style/size change.

Reasons for Reoperation
You should provide the cumulative reasons for reoperation for each separate patient cohort at each timepoint. The denominator should be the total number of reoperations since the initial implantation to that timepoint. If more than one reason for the reoperation is reported, then you should report all reasons.

Types of Additional Surgical Procedures
You should provide the cumulative types of additional surgical procedures for each separate patient cohort at each timepoint. The denominator should be the total number of additional surgical procedures since the initial implantation to that timepoint. If more than one type of procedure is reported, then you should report all procedures performed.

Kaplan-Meier Analyses of Complications Occurring After Implant Removal With Replacement

You should provide the Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on a per device basis for each separate patient cohort and for the total population for every complication occurring after implant removal with replacement. You should use the date of implant replacement as the beginning timepoint for this analysis.

9.5 Safety Data Presentation - CTDs

CTD Diagnosis

CTD diagnoses include those listed as "rheumatic diseases" or "rheumatic syndromes" in Section 8.3 of this guidance document. You should provide the following data on a per patient basis for each separate patient cohort and the total population:

- Kaplan-Meier analyses (e.g., 1 minus the Systemic Lupus Erythematosus-free survival rate over time) for each CTD diagnosis separately and for having one or more CTD diagnosis
- the cumulative incidence of CTD diagnoses at each timepoint for each CTD diagnosis separately and for having one or more CTD diagnosis. You should provide the numerator and denominator used. You should describe how these values were obtained. The denominator is the number of patients at that timepoint.

CTD Signs/Symptom Categories

A symptom category is defined as an anatomical or body function area (e.g., Skin, Muscle, Joint, Neurological, General). For example:

- Skin includes alopecia, facial rash, pruritis, and echymoses
- Muscle includes myalgias, muscle weakness, and elevated CPK
- Joint includes arthralgia, arthritis, and morning stiffness
- Neurological includes cognitive dysfunction, memory problems, and multiple sclerosis-like symptoms
- General includes fatigue, generalized pain, and fever.

For each symptom category above, you should provide the following data on a per patient basis for each separate patient cohort and the total population:

- Kaplan-Meier analyses (i.e., the CTD symptom category-free survival rate over time) for each symptom category separately and for having one or more positive symptom category. (A positive symptom category is defined as one or more symptoms reported in that category.)
- the cumulative incidence of at least one symptom per symptom category at each timepoint for each symptom category separately and for having one or more positive symptom category. You should provide the numerator and denominator used and describe how these values were obtained. The denominator is the number of patients at that timepoint.

CTD Signs/Symptoms

For each rheumatic sign/symptom or other reported sign/symptom described in Section 8.3, you should provide the following data on a per patient basis for each separate patient cohort and the total population:

- the non-cumulative point prevalence of CTD signs/symptoms at each timepoint for each CTD sign/symptom separately and for having one or more positive CTD sign/symptom
- the cumulative incidence of CTD signs/symptoms at each timepoint for each CTD sign/symptom separately and for having one or more CTD sign/symptom. You should provide the numerator and denominator used and describe how these values were obtained. The denominator is the number of patients at that timepoint.

9.6 Safety Data Presentation – Silent Rupture

You should provide analyses for each occurrence of the following silent rupture events:

- MRI diagnosis of suspicious or definitive rupture (refer to Section 8.3) regardless of confirmation with removal
- rupture noted at removal regardless of MRI diagnosis
- rupture noted at removal for explanted patients or MRI diagnosis of rupture without removal.

The analyses for each silent rupture event should include:

- Kaplan-Meier analyses on both a per patient and a per device basis for each separate patient cohort and the total population
- the cumulative incidence at each timepoint on both a per patient and per device basis for each separate patient cohort and the total population. You should provide the numerator and denominator used. You should describe how these values were obtained. The denominator is the number of patients or devices at that timepoint.

9.7 Safety Data Presentation - Mammography Data

For patients who undergo screening mammography during the study, you should provide separate analyses for each of the following events:

- mammographic suspicion for tumor regardless of biopsy results
- mammographic suspicion for tumor with a biopsy positive for malignant tumor
- mammographic suspicion for tumor with a biopsy negative for malignant tumor.

The analyses for each event should include:

- the non-cumulative point prevalence at each timepoint on both a per patient and per device basis for each separate patient cohort. You should provide the numerator and denominator used. You should describe how these values were obtained. The denominator is the number of patients or devices at that timepoint.

- the cumulative incidence at each timepoint on both a per patient and per device basis for each separate patient cohort. You should provide the numerator and denominator used. You should describe how these values were obtained. The denominator is the number of patients or devices at that timepoint.
- a comparison of the data obtained in the non-cumulative point prevalence and the cumulative incidence analyses with that reported in the literature for aged-matched cohorts.

9.8 Effectiveness Data Presentation

Anatomical Effect

You should provide the frequency distribution of bra cup size at baseline, end of study, and change from baseline. You should report these results on both a per patient and per device basis for each separate patient cohort.

You should provide mean, median, and mode (± standard deviation) chest circumferences at baseline and at the end of the study, as well as the change. You should report these results on a per patient basis for each separate patient cohort.

For the augmentation cohort, you should provide a matched two-way table of the number of patients in each cell demonstrating a change in bra cup size from before to after. The table should include the before-values on the columns and after-values on the rows with each cell representing the number of patients with a change from each category before to after.

HRQL

You should provide the mean (± standard deviation) change in each validated measure (preoperative to each visit). You should report these results on a per patient basis for each separate patient cohort. The denominator is the number of patients at each visit. FDA also recommends that you compare your results to published normative data for SF-36.

9.9 Pooling Analyses

You should demonstrate that the patients in the study are representative of the population for whom the device is intended by providing the statistical rationale for pooling across:

- investigational site
- demographic and baseline characteristics described in Section 9.3 above.

9.10 Additional Analyses

Logistic Regression Analyses of Each Safety and Effectiveness Outcome

To determine which variables are associated with each safety and effectiveness outcome, you should provide logistic regression analyses, where appropriate, on a per device basis for each separate patient cohort using, at minimum, the following static covariates:

- patient age
- indication for use (i.e., augmentation vs. reconstruction vs. revision)
- device surface type (i.e., smooth vs. textured)
- device type (i.e., single vs. multi-lumen), if applicable

- device style and/or size, if clinically relevant
- valve type (e.g., leaf, diaphragm), if applicable
- surgical incision site (e.g., periareolar, inframammary fold, axillary)
- incision size
- device placement (e.g., retromuscular, subglandular)
- timing of reconstruction (i.e., immediate vs. delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents, if applicable.

Cox Proportional Hazards Regression Analyses of Rupture/Deflation

To determine which variables are associated with rupture/deflation, you should provide Cox regression analyses of rupture/deflation on a per patient basis for each separate patient cohort using the static covariates above, as well as time-dependent covariates (e.g., infection, capsular contracture). The coefficient estimates are relative risks (hazard ratios) of rupture/deflation based on transition to a complication. An advantage of this approach is that the rupture/deflation is quite clearly defined and multiple complications can be easily handled as separate time-dependent covariates for each type of event. This also addresses the problem of competing risks.

10. Labeling

10.1 General Information

General labeling requirements for medical devices are described in 21 CFR 801. Additional sources of labeling requirements are 21 CFR 812.5, 812.7, and 812.20(b)(10) for an IDE and 21 CFR 814.20(b)(10) for a PMA. Both the IDE and PMA regulations require that you provide copies of all labeling. Additional labeling recommendations may be obtained from the guidance document, "**Device Labeling Guidance #G91-1,**" http://www.fda.gov/cdrh/g91-1.html.

Although the content within a piece of labeling may change from that provided in an IDE as compared to that provided in a PMA, you should provide package labels, a patient device card/sticker, a package insert, and patient information, at minimum, for any IDE or PMA.

When developing the labeling, you should refer to the FDA breast implant consumer handbook entitled, "**Breast Implants – An Information Update**" for additional information, such as risks and factors to consider. This handbook, as well as additional breast implant information, is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

10.2 Package Labels

You should include copies of all labels used in the packaging of your device. You should also include a description of where each label is attached or included in the packaged device.

The outer package label(s) should include, at minimum, the following information:

- device name, style, etc.

- device serial/lot number
- name and address of manufacturer, packer, or distributor
- quantity
- material
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date.

If the breast implant is being studied under an IDE study, then the package label(s) must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR 812.5)

10.3 Device Card

This piece of labeling has been referred to in different ways by manufacturers, such as manufacturer device card, patient identification card, or patient information card. However, the sole purpose of it is to provide the patient with specific information about the device(s) implanted. Typically, multiple device labels/stickers are included in the device package along with the device card. At the time of surgery, one label/sticker should be placed in the patient's records and the one label/sticker should be placed on the device card. Otherwise, the physician/surgeon should complete the device card him/herself. This device card should be given to the patient immediately following surgery. This device card should include, at minimum, each implant's style, size, and serial/lot number.

10.4 Package Insert

The package insert for a breast implant typically involves a combination package insert/surgical technique manual. However, you may choose to provide this information in separate pieces of labeling. As a collective piece of labeling, you should include the following type of information:

- device name, style, etc.
- name and address of manufacturer, packer, or distributor
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- expiration date
- brief device description with material information
- indications for use
- any relevant contraindications (including surgical procedures which are contraindicated due to interference with implant integrity and/or performance), warnings, and precautions
- list of potential complications
- procedures such as descriptions how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and troubleshooting procedures
- instructions for implantation, including surgical approach and device specific information (depends on type of breast implant)

- intraoperative test procedures to ensure implant integrity and proper placement (if necessary)
- instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period and during any subsequent surgical procedures, postoperative patient care, etc.
- how to evaluate, and how often to evaluate, implant integrity and placement.

For an IDE package insert, you must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR 812.5)

For a PMA package insert, you should include appropriate study safety and effectiveness results in addition to the bulleted items above.

You should make the package insert available to the patient prior to the surgery, upon request, whether the request comes directly from the patient or through the physician/surgeon.

10.5 Patient Information

For an IDE study, one form of patient information is the required informed consent document (21 CFR 50). You may provide additional patient labeling for an IDE study other than the required informed consent document. Note that the informed consent document required for a patient to participate in an IDE study should not be confused with a standard surgical consent form that a hospital requires to be signed by any patient.

For a PMA-approved breast implant, patient information is in a form of what is generically referred to as patient labeling, patient brochure, or patient booklet.

The ultimate purpose of the patient information is to provide the patient with sufficient information so that she may make an informed decision as to whether to receive breast implants. Therefore, it is imperative that a patient receive the patient information at the initial visit/consultation so that she has sufficient time to review the information and discuss any issues with her physician/surgeon as part of her decision making process.

The IDE informed consent document describes the purpose of the clinical study, the potential risks, etc. The specific elements required in an informed consent document are described in 21 CFR 50.25. You should include any other appropriate elements identified from the bulleted list for the patient labeling below.

The patient information developed for a PMA-approved breast implant or as supplemental information for an IDE study should include the information needed to give prospective patients realistic expectations of the benefits and risks of breast implant surgery. You should include the following information, at minimum, in the patient labeling/patient brochure:

- device names, styles, etc.
- brief device description with material information

- indications for use
- relevant contraindications, warnings, and precautions
- potential complications, including the possible methods of resolution
- anticipated benefits
- surgical alternatives, including no treatment or no implants and the benefits and risks of each
- postoperative care, including what to expect after surgery, symptoms to tell doctor about immediately, length of recovery, physical limitations, etc.
- factors to consider in the decision whether or not to get implants (e.g., may not be "lifetime" implant or one-time surgery, many of the changes to your breast following implantation are irreversible, breast implants may affect your ability to breast feed, routine screening mammography will be more difficult, health insurance coverage issues)
- other factors to consider (e.g., choosing a surgeon, implant size and shape, surface texturing, palpability, implant placement, incision sites)
- additional information related to the device such as lifetime replacement and reimbursement policy information, including estimated cost for replacement, costs not covered, etc.
- study safety and effectiveness results.

IDE and PMA patient information should not exceed the reading comprehension level that is easily read and understood by most readers in the United States. You should keep technical terms to a minimum and define any that are used. For additional information, you should refer to "**Guidance on Medical Device Patient Labeling**" at http://www.fda.gov/cdrh/ohip/guidance/1128.pdf and our information regarding plain language at http://www.plainlanguage.gov.