Guidance for Industry and FDA Staff

Saline, Silicone Gel, and Alternative Breast Implants

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. When submitting comments, please refer to Docket No. 2004D-0002. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Saline, Silicone Gel, and Alternative Breast Implants

This guidance represents the Food and Drug Administration's (FDA'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 FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

1. Introduction

This guidance document identifies the device description, preclinical, clinical, and labeling information we recommend you present in a premarket approval application (PMA) for a breast implant. This guidance document may also be useful in preparing an application for an investigational device exemption (IDE). This document addresses breast implants filled with saline, silicone gel, or alternative filler intended for breast augmentation or breast reconstruction. This guidance document does not address tissue expanders, which are reviewed under the premarket notification (510(k)) process.

In January 2004, FDA issued a draft update to the 2003 version of this guidance document and received over 50 comments. The changes to the 2004 draft involved the mechanical data, modes and causes of rupture, clinical data, and labeling sections. Now, FDA is updating to this guidance document to reflect the latest thinking in science and medicine on breast implants based on the April 2005 General and Restorative Devices Panel meeting, FDA's review of two silicone gel-filled breast implant PMAs, and comments received on the 2004 draft guidance document. The primary changes to the guidance document since the 2004 draft version are to the **Mechanical Data, Device Explant Analyses** (formerly Modes and Causes of Rupture), **Core Study Clinical Data**, and **Postapproval Requirements** sections. FDA also combined the former two clinical sections into one section.

This guidance document supplements other FDA publications on PMA and IDE applications and should not be construed as a replacement for these documents. For general information about these applications, see CDRH's Device Advice website as follows:

- PMAs (21 CFR Part 814), http://www.fda.gov/cdrh/devadvice/pma/
- IDEs (21 CFR Part 812), http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

Sponsors are responsible for developing clinical protocols and providing reasonable assurance of the safety and effectiveness of their devices.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance 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

Saline-filled, silicone gel-filled, and alternative breast implants may be indicated for breast augmentation and/or breast reconstruction, which are defined as follows:

- Breast augmentation. Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of an original primary breast augmentation surgery (i.e., revision-augmentation).

- Breast reconstruction. Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the result of an original primary breast reconstruction surgery (i.e., revision-reconstruction).

However, as discussed later in this document, we recommend you collect clinical data for each of the individual indication subgroups of primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction.

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. The sterile saline used as a filler material should follow United States Pharmacopeia (USP) standards for Normal Physiological Saline (injection grade),

which has a concentration of 0.15M and a pH of 7.2-7.4.

There are currently three types of designs for saline-filled breast implants:

- a fixed volume implant with a single lumen that is intraoperatively filled with the entire volume of saline via a valve
- 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 volume
- a prefilled saline implant.

In the Federal Register of June 24, 1988 (53 FR 23856), FDA issued a final rule 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 submission of PMAs for these devices. On January 8, 1993 (58 FR 3436), FDA issued a proposed rule to require submission of PMAs or completion of product development protocols (PDPs). On August 19, 1999 (64 FR 45155), FDA issued a final rule requiring PMAs for these devices to be filed with FDA, or PDPs to be completed, within 90 days. Thus, an approved PMA or PDP is now required to market a saline-filled breast implant.

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.

There are currently three types of designs for silicone gel-filled breast implants:

- a fixed volume implant with a single lumen containing a fixed amount of silicone gel
- 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
- 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 of saline volume.

In the Federal Register of June 24, 1988 (53 FR 23856), 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 submission of PMAs for these devices. On May 17, 1990 (55 FR 20568), FDA issued a proposed rule to require submission of PMAs or completion of PDPs. On April 10, 1991 (56 FR 14620), FDA issued a final rule requiring PMAs for these devices to be filed with FDA, or PDPs to be completed, within 90 days. Thus, an approved PMA or PDP is now required to market a silicone gel-filled breast implant.

2.3 Alternative Breast Implant

An alternative breast implant is not a saline-filled breast implant or a silicone gel-filled breast implant, as defined above. Instead, 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 made from a material other than silicone rubber. We may recommend different or additional evaluations of alternative breast implants depending on their design, materials, and performance characteristics.

All alternative breast implants are class III post-amendment devices that require an approved PMA or PDP for marketing. (Federal Food, Drug, and Cosmetic Act (FDCA) §§ 513(f) and 515(a) (21 U.S.C. §§ 360c(f) & 360e(a)).)

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 recommends the type of device description information you should include in your application. However, depending on the particular design of your device, additional information may be appropriate.

We recommend you provide the following device description information (as applicable):

- the type of implant, as described in the **Background** section (e.g., a fixed volume, single lumen silicone gel-filled breast implant)
- a written description of each component that comprises the device (e.g., shell, gel, patch, textured surface, valve)
- the specific materials (with suppliers) used to manufacture each component
- a description of any connector systems, fill tubes, and injection domes, including materials and a magnified sketch depicting their placement/use
- a description of when the device is filled by the surgeon if it is not a prefilled device (i.e., intraoperatively and/or postoperatively)
- a description of any overexpansion/overfill of the filler material, even if on a temporary basis (e.g., a range of saline filler allowed for a given size implant)
- a description of the method used to sterilize the device
- a summary table of all device styles under review in the submission (see example table below):

Style	Shell Surface	Shape, Profile	Volume (cc)	Width (cm)	Height (cm)	Projection (cm)	Shell Thickness (mm)
XXXX	Smooth	Round, High	125-650	9-16	8.4-15	3.1-5.7	0.015"-0.040"

Depending on the specific design features of your device, we may recommend you include additional information and/or columns in your summary table.

4. Chemistry Data

4.1 General Information

For the chemicals and materials used in the manufacture of your breast implant, we recommend you provide the:

- common names and trade names of each chemical/material (including additives, plasticizers, and antioxidants)
- specific role of each chemical and material in the manufacturing process and/or in the final device
- location of the material within the device (e.g., shell, filler, valve, adhesive)
- 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, as well as a signed letter from the MAF owner granting you permission to use its data, if applicable.

We also recommend you state whether the silica used in the elastomer shell dispersion is in the amorphous form or the crystalline form.

Sections 4.2 through 4.5 of this document describe chemical analyses of the elastomer shell (including the patch and valve) that we recommend you include in your submission. Sections 4.6 through 4.9 describe chemical analyses of the filler material. Additional analyses may be appropriate depending upon the design features of your device, such as texturing, variations in device components (such as patches or valves), or the sterility methods used.

4.2 Extent of Crosslinking

The manufacture of the shell involves curing of polymeric components of silicones by chemical crosslinking. We recommend you provide the extent of crosslinking from at least three different manufacturing lots to confirm the uniformity of the degree of crosslinking across lots. Suggested methods to determine the extent 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 an appropriate solvent similar to that used for the extractable analyses
- determination of the amount of unreacted crosslinker from the total extractables.

We recommend you also perform an analysis on the cured polymer to confirm the presence of silicone functional groups. One recommended method is Fourier Transform Infrared Spectroscopy (FTIR).

4.3 Extractables

We recommend you conduct an analysis of the extractables or releasable chemicals obtained by exhaustive solvent extraction to identify potentially toxic chemicals and estimate the upper limits of the chemicals that could be released into the patient. Soxhlet extraction is one recommended method. Below is a general description of a protocol for attaining exhaustive extraction of extractables or releasable chemicals.

> Perform the extraction of the shell for chemical analyses with at least one polar solvent (e.g., ethanol or a mixture of ethanol-water) and two non-polar solvents (e.g., dichloromethane and n-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, you should apply the test to the contents of the extract with molecular weights of ≤1500 Daltons because these are the compounds of greatest clinical interest. You should 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.

We recommend you provide the following information from your analyses of the extractables:

- identification and quantification of all compounds with molecular weights of ≤1500 Daltons after exhaustive extraction of the final sterilized shell. These should include, but need not be 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]
- 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

We recommend you analyze the elastomer shell for volatile components using a headspace detector.

4.5 Heavy Metals

We recommend you provide qualitative and quantitative analyses for heavy metals on the final finished shell. The heavy metal analyses should include, but need 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, we recommend you 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 device should follow USP standards for 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 to be filled with any other saline, we recommend you provide a complete chemical analysis of that saline.

4.7 Silicone Gel Filler

The analyses of the silicone gel should be very similar to those for the elastomer shell. For the final sterilized gel, we recommend you provide the:

- qualitative and quantitative analyses for extractables (such as cyclic polysiloxanes), including:
  - characterization of the polymers present
  - molecular weight averages and polydispersities of the polymers

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[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.

  - identification and quantification of all compounds present with molecular weights ≤1500 Daltons
- qualitative and quantitative analyses for volatiles
- qualitative and quantitative analyses for heavy metal contents
- physical properties of the gel, including viscosity, cohesivity, and approximate crosslink density (if possible)
- percentage of silicone oil and its chemical and physical properties (e.g., molecular weight, viscosity).

4.8 Alternative Filler - Polymer

For the final sterilized, alternative polymer filler, we recommend you provide the:

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

4.9 Alternative Filler – Non-Polymer

For the final sterilized, alternative non-polymer filler, we recommend you provide the:

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

- source and isolation procedure of the non-polymer
- structural analyses of the non-polymer, including molecular weight distribution.

5. Toxicology Data

5.1 General Information

We recommend you provide a toxicological assessment because breast implants contain not only the major polymeric materials (e.g., polymerized polydimethylsiloxane), but also low molecular weight components (e.g., D_4) from the manufacturing or sterilization processes that may leach out into the patient's body. In addition to the chemical composition information (Section 4.1 above), the toxicological safety assessment should include information from pharmacokinetic studies and toxicological testing, as described below.

5.2 Pharmacokinetic Studies

Knowledge of the pharmacokinetic behavior of potentially toxic chemicals is a scientific assessment of the potential of the chemicals to accumulate in the body at concentrations that cause human health risks. Your pharmacokinetic study design should address the worst case assumption (i.e., all of the material in the device 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 device into the body, or rapid metabolism or excretion of the substances by the patient, may negate the worst case assumption. The pharmacokinetic testing of toxicants 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, we recommend you label the device to reflect the fates of all of the components of interest. For additional information about pharmacokinetics, refer to ISO 10993 - Part 16.[3]

5.3 Toxicological Testing

Toxicological testing is used to detect unidentified toxicants and to quantify the exposure to known toxic compounds. We recommend you perform the following toxicological tests separately on both the final sterilized shell and filler:

- cytotoxicity
- acute systemic toxicity
- hemocompatibility
- immunotoxicity
- reproductive toxicity

[3]ISO 10993 - Part 16, "Biological evaluation of medical devices – Part 16: Toxicokinetic study design for degradation products and leachables," International Organization for Standardization (ISO).

- teratogenicity
- genotoxicity
- carcinogenicity
- implantation testing.

Refer to ISO 10993 – Part 1[4] and the CDRH 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. We have included additional special considerations for some of these tests below.

Acute Systemic Toxicity
For the pyrogenicity element of the acute systemic toxicity testing, we recommend that you perform both the rabbit pyrogen and the Limulus Amebocyte Lysate (LAL) tests. For routine batch monitoring, the LAL test should be sufficient.

Immunotoxicity Testing
For immunotoxicity testing, we recommend you assess the level of immunotoxicity of the shell and any leachable compounds from the shell and the gel (if applicable). 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 Testing
For reproductive and teratogenicity testing, you should measure the rates of conception, maturation, and cycling abnormalities, as well as the number of fetal deaths and malformations. Obvious malformations are rare; therefore, we recommend extensive examinations to adequately assess the malformation rates. 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 Testing
For genotoxicity testing, you should address the potential of leachable compounds and/or degradation products of your device to cause cancer. The short-term genotoxicity testing should consist of:

- a bacterial mutagenicity test (including point mutations and frameshift mutations)
- a mammalian forward mutation assay (e.g., a mouse lymphoma test)
- an in-vivo rodent micronucleus test.

Genotoxicity testing may be sufficient in lieu of 2-year carcinogenicity testing, if all of the short-term genotoxicity testing is negative. However, even if the short-term genotoxicity

[4] ISO 10993 – Part 1, "Biological evaluation of medical devices – Part 1: Evaluation and testing," International Organization for Standardization (ISO).

testing is negative, FDA may still recommend 2-year carcinogenicity testing if your device consists of other materials than those typically present in polydimethylsiloxane-based breast implants or material compounds (e.g., D_4) at higher than expected levels.

Implantation Testing

We recommend you provide acute, subchronic, and chronic implantation testing because some implant components may elicit immediate tissue reactions, while others may diffuse out of the device slowly and/or undergo chemical changes that affect the surrounding tissues long after implantation. You should implant samples of shell and gel, as well as a standard control (e.g., polyethylene), subcutaneously or submuscularly. We do not recommend that you use extracts. You should report the gross and histological observations of the effects of implantation. We recommend that the chronic implantation testing be extended for 2 years, roughly the lifetime of the rat.

If the short-term genetic toxicology testing is negative and the clinical carcinogenic experience with the materials continues to support safety, it may be appropriate to complete the carcinogenicity testing and/or chronic implantation testing concurrently with an ongoing clinical study.

6. Mechanical Data

6.1 General Information

We recommend you provide mechanical testing on the final finished product or individual components of it (e.g., shell, valve). These tests are described in Sections 6.2-6.7 below. Whenever possible (and applicable), testing should mimic in-vivo conditions. If your device is sterilized by different methods (e.g., ethylene oxide, gamma radiation), you should perform the testing on samples sterilized by the different methods, or provide an adequate rationale why the change in sterilization method does not negatively impact the mechanical characteristics. You should also provide complete reports for all testing, including identification of the devices tested and a description of the test set-up and methods, including sketches or photographs.

6.2 Fatigue Rupture Testing of Total Device

Most materials have a finite fatigue life when repeatedly stressed in-vivo. Repeated stressing of the device may eventually weaken the shell and lead to failure. While FDA recommends a test method that mimics in-vivo conditions, FDA recognizes that a test method cannot be adequately validated until in-vivo rupture from cyclic fatigue has been analyzed and characterized. Currently available data on retrieved devices implanted for approximately 10 years suggest that the devices may be failing due to reasons such as fold flaw, localized shell stress, and instrument damage, rather than shell rupture due to pure cyclic loading. Nevertheless, FDA believes that cyclic testing provides useful information about the fatigue characteristics of the device.

Therefore, we recommend you provide a complete test report of fatigue testing on the worst case, final, sterilized device(s) with the thinnest shells allowed by the design release criteria using a test set-up with particular focus on the loading direction(s) on the device, the shape of the loading apparatus that contacts the device, and the testing medium, etc., that best mimics expected in-vivo loading. The common test methodology, in which flat plates compress the device, may or may not be predictive of clinical failure for your device.

We recommend you perform fatigue testing in a constant load or a constant displacement mode. However, you should perform constant displacement testing only 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. You should use the minimal load applied during constant displacement testing to establish the endurance load level.

You should cyclically load the samples at varying loads or displacements to generate an applied force versus number of cycles to failure (AF/N) curve for each style of device tested. You should test a minimum of 3 samples from a typical production run at a given load or displacement because of the general variance seen in elastomer testing. We recommend the endurance load (or the load at which the samples do not fail under cyclic loading) be established at a minimum of 6.5 million cycles runout. The AF/N curves may be generated by best-fit approach or by averaging the number of samples tested at each load. There should be a tight range (e.g., 10%) of points around and at the endurance load level for an optimal estimate of fatigue strength.

We recommend you provide the following results for each style of device tested:

- the resulting endurance load level
- the clinical relevance for the resulting endurance load level
- the AF/N curve
- the raw data (e.g., applied loads, applied displacements for displacement control test, number of cycles to failure, sample thicknesses).

In addition to the fatigue testing described above, we recommend you perform an analysis of the cyclic raw data to estimate a pure cyclic fatigue lifetime of your device. However, FDA believes that this will remain unvalidated until you have analyzed and duplicated clinical failures from pure cyclic fatigue in bench testing.

6.3 Valve Competency Testing

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. Devices 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 devices.

ASTM standard F2051[5] 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 ASTM F2051 methodology is clinically relevant with respect to the load levels. However, this methodology may provide useful information about the valve's response to shifts in pressure. Therefore, we recommend you provide a complete report of valve competency testing, as described in ASTM F2051 or an equivalent method, with pass/fail results for leakage.

In addition to the testing above, you should provide a complete report of destructive testing to address in-vivo loading conditions. You should gradually load the samples until valve failure occurs to define a maximum pressure for the device. We recommend you provide the:

- burst pressures
- failure modes (including whether the failed test valves reseal upon removal of the excess failure-inducing pressures)
- rationale why the resulting burst pressures are clinically relevant.

6.4 Cohesivity Testing

This testing pertains only to silicone gel-filled and, possibly, alternative breast implants.

Cohesivity of Silicone Gel-Filled Breast Implants

We recommend you quantify the cohesivity of the silicone gel. Although the two methods described in ASTM F703[6] were not developed to address gels with high cohesivities, we believe the results provide useful device characterization information. We recommend you provide complete reports of the following testing to address gel cohesivity:

- gel cohesion testing on the final gel as described in the cone/pendant method in ASTM F703 and provide the pass/fail results
- penetration testing (an indirect measure of gel cohesivity) on the in-process gel and provide a complete description of the penetration test method, the acceptance criteria, and the results.

Cohesivity of Alternative Breast Implants

Depending on the filler used in your alternative breast implant, FDA may recommend a different method to assess cohesivity than described above for silicone gel-filled breast implants.

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[5] ASTM F2051, "Standard Specification for Implantable Saline Filled Breast Prosthesis," ASTM International.

[6] ASTM F703, "Standard Specification for Implantable Breast Prostheses," ASTM International.

6.5 Bleed Testing

This testing pertains only to silicone gel-filled and alternative breast implants.

Bleed of Silicone Gel-Filled Breast Implants

Silicone gel bleed is the diffusion of gel constituents through an intact shell. It is important to assess gel bleed for your silicone gel-filled breast implants in order to have information accurately characterizing the gel bleed of your product, which can be included in your labeling.

The ASTM F703 test is one method to evaluate the extent of gel bleed. However, the results from this testing have limited clinical correlation because the ASTM F703 test method was established for the purpose of allowing comparison between device models rather than quantifying in-vivo gel bleed. In addition, the ASTM F703 test method was not established to identify and quantify gel bleed constituents. Thus, FDA does not believe that this test methodology provides adequate data to address gel bleed for the purposes of a PMA.

Accordingly, we recommend you provide a complete report of gel bleed bench testing based on a protocol that mimics in-vivo conditions. That is, you should incubate (immerse) the breast implants in a medium that simulates the known composition of human interstitial fluid.[7] Animal serum that approximates this composition or any artificial medium with a composition similar to interstitial fluid may be acceptable. Because the in-vivo environment is dynamic, you should allow for transfer of new medium to prevent saturation. The testing should continue until the change in gel bleed rate of the detectable gel constituents has leveled off. We recommend you identify the gel bleed constituents (including silicones and platinum species (or other catalysts)), the rate that these gel constituents bleed out, and how that rate changes over time.

FDA understands the limitations of this gel bleed bench testing in mimicking the in-vivo environment, as well as the limitations of how these data correlate with clinical use. Nevertheless, we believe this testing is a step closer to more accurately characterizing gel bleed than the existing ASTM F703 test methodology. If you believe that you have an alternative method (e.g., animal study) or clinical data that identifies and quantifies the gel bleed constituents over time, we recommend you contact FDA.

Bleed of Alternative Breast Implants

For devices with alternative fillers, FDA is concerned about potential changes in the composition of the alternative filler resulting from long-term chronic bleed. Therefore, in addition to performing the testing described above for a silicone gel-filled breast implant, we recommend you provide the results of a chemical analysis of the material remaining in the device, over time, when evaluated in a test that mimics in-vivo conditions.

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[7] Fogh-Andersen, N, BM Altura, BT Altura, and OS Siggaard-Andersen: Composition of Interstitial Fluid, Clin Chem (41/10), 1522-1525 (1995).

6.6 Stability Testing of Alternative Breast Implants

Whereas silicone polymers (e.g., silicone gel) are considered to be highly stable, the stability characteristics of an alternative polymer or non-polymer filler may be unknown. Therefore, for a breast implant with an alternative polymer or non-polymer filler, we recommend you provide a complete report of stability/aging testing to demonstrate the effects of time and temperature (physiological temperature (37°C) and elevated temperature (≈60°C)) 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.

6.7 Shelf Life Testing

We recommend you provide both real-time mechanical testing and packaging testing to establish the shelf life (i.e., expiration date) for the device. Accelerated shelf life testing may be appropriate if it has been validated by real-time data.

Mechanical Testing

We recommend you perform mechanical testing on representative aged samples at time zero and at various intervals throughout the shelf life. The mechanical tests should include, but need not be limited to:

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

Packaging Testing

With regard to packaging testing, we recommend you 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. Below is a more detailed description of what we recommend you provide to address initial package integrity and maintenance of package integrity.

Initial Package Integrity

We recommend you test the integrity of the seal and the whole package at time zero. This includes both seal and whole package testing. You should test the seals of the package 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[8] is a dye penetration method for

[8] ASTM F1929, "Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging

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. Currently, there are only a few standardized physical whole package test methods. ASTM D3078[9] is an example of a test method by bubble emission. Alternatively, a microbial challenge test may be appropriate.

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

7. Device Explant Analyses

You should provide device explant analyses with the goal of characterizing modes and causes of device failure and potentially minimizing the identified failures. In order to provide as large a sample as possible, we recommend that the analyses include any available explanted devices, such as those from the European market, as long as they are the same devices for which you are seeking PMA approval.

7.1 Retrieval Study

We recommend that you perform a retrieval study as the primary means of evaluating all available explanted devices. A standard retrieval study should involve:

- data collection at the time of explantation by the surgeon or appropriate healthcare provider
- laboratory analysis/testing of the explanted devices by you or a third party.

If the retrieval study involves explants from the Core Study (i.e., the primary IDE study used to support PMA approval), FDA may also request that you provide some Core Study clinical data, such as complication and MRI data, that correspond to the patients with explants to better understand the results of the laboratory analyses.

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by Dye Penetration," ASTM International.

[9] ASTM D3078, "Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission," ASTM International.

Data at Time of Explantation

We recommend the following observations be recorded on a field report form by the explanting surgeon or appropriate healthcare provider at the explant site:

- reason(s) for the device explantation
- relevant device observations at explantation, for example:
  - presence of any shell defects, such as a hole or tear
  - presence and extent of implant rupture (intracapsular gel, extracapsular gel, or migrated gel)
  - the condition of the valves and/or patches
  - any discoloration of the filler
  - fungal or bacterial contamination in shell or within filler
- if applicable, whether implant rupture is believed to have occurred before or during explantation.

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

Laboratory Analyses/Testing

We recommend you provide laboratory analyses/testing on all available explanted devices, whether or not the explanted device is identified by the explanting party as being ruptured, in order to characterize the modes and causes of failure from the available explanted devices. While rupture (or shell opening) is one example of a failure, any undesirable change to the device should also be characterized as a failure (e.g., gel fracture of the more-cohesive silicone gel-filled breast implants).

As part of the laboratory analyses/testing, FDA recommends you provide thorough visual and microscopic examination findings of all available explanted devices and physical property testing to assess trends, to address retrieval study findings, etc.

FDA recommends you consider the article by Brandon, et al.[10] for a description of the type of analyses/testing that may be appropriate for your retrieval study (e.g., control group of unimplanted devices, detailed chemical analyses of materials, detailed mechanical testing, scanning electron microscopy, and analysis of local tissue/capsule).

You should also consider the impact of the following factors when characterizing the modes and causes of failure of your device:

- device type/model, lot number, size, shell thickness, surface type (smooth or textured)
- implantation duration

[10] Brandon, et. al, "Protocol for Retrieval and Analysis of Breast Implants." Journal of Long-Term Effects of Medical Implants, 13(1): 49-61. 2003.

- device handling prior to insertion
- device position (subglandular or submuscular)
- incision size
- observations recorded at the time of explantation (section above)
- surgical damage during implantation (scalpel nicks, suture punctures, surgeon's finger imprints, clamp grip marks)
- in-vivo trauma (accident, mammography)
- procedures performed while device is in-situ (biopsies, cyst aspirations)
- explantation technique
- in-vivo material property and chemistry changes or degradation.

7.2 Supplemental Information to Characterize Device Failure

To further characterize the modes and causes of failure of your device, we recommend you provide:

- an assessment of your manufacturing processes related to release specifications of your shell to determine whether any allowances for imperfections, such as bubbles and contaminants, may be related to device failure
- an assessment of the surgical techniques that may increase the risk of rupture
- a comprehensive literature review of durability studies based on explanted devices
- any additional appropriate studies to asses the modes and causes of device failure.

FDA believes that this information may be used to design preclinical tests that are more predictive of the long-term rupture rate. We recommend that you also use the results to design improved devices and establish new manufacturing acceptance criteria.

8. Core Study Clinical Data

8.1 General Information

Indications

We recommend that the Core Study (i.e., the primary IDE study used to support PMA approval) include separate patient cohorts of:

- primary augmentation
- primary reconstruction
- revision-augmentation
- revision-reconstruction.

Because these studies are complicated by the fact that an individual patient may receive two devices for two different reasons (e.g., a woman may receive one device for reconstruction and one for augmentation), we recommend you record and analyze the data on both a per patient and a per device basis.

We recommend you classify the patient and device by the initial indication at study *entry* as follows:

- If a reconstruction patient undergoes contralateral augmentation, you should classify that *patient* as reconstruction. The *device* should be classified as one reconstruction and one augmentation.
- If a revision-augmentation patient (i.e., the patient entered the study due to replacement of an existing device, regardless of the type or manufacturer of the existing device), undergoes contralateral augmentation, you should classify that *patient* as a revision-augmentation patient. The *device* should be classified as one revision-augmentation and one augmentation.
- Even if the device is removed and replaced during the study (i.e., after initial implantation), you should classify the *patient* and *device* under the original indication (i.e., primary augmentation, primary reconstruction, or revision-augmentation or revision-reconstruction).

Core Study Duration

FDA recommends that the Core Study involve 10 years or more of prospective patient follow-up, including some premarket and some postmarket follow-up. The premarket duration of the Core Study will depend on the device design and all of the available safety and effectiveness data, including, but not limited to, the Core Study data. As a whole, the premarket data (clinical and preclinical) should be sufficient to characterize complication rates over time, potential health consequences of those complications, and any other specific safety concern for your device, whether it is a saline-filled, silicone gel-filled, or alternative breast implant.

Section 9 of this document describes how additional information to address issues associated with silicone gel-filled breast implants may be addressed by clinical data other than the Core Study. In addition, Section 9 describes how literature may provide supplemental information to address specific breast implant topics.

At this time, a minimum of three years of premarket Core Study data have been submitted to support approval of standard silicone gel breast implants, and a minimum of two years of premarket Core Study data have been submitted to support approval of standard saline-filled breast implants. However, the appropriate length of time for collection of premarket Core study data will be determined on a case-by-case basis for each implant after careful consideration of all available clinical and preclinical data.

Evaluation Timepoints
FDA recommends that you conduct regularly scheduled evaluations of complications, with follow-up intervals of 6-10 weeks, 1 year, and annually through 10 years. We recommend you perform annual evaluations to minimize the number of patients lost-to-follow-up.

For MRIs to screen for asymptomatic (silent) rupture (see Section 8.5), connective tissue diseases evaluations (see Section 8.6), and patient reported outcome evaluations (Section 8.8), we recommend biennial follow-up evaluations.

Follow-up after Device Removal
For patients who undergo device removal and replacement with your device or removal without replacement, you should continue to collect safety data on these patients as described in your protocol.

Control Group
If you choose to incorporate a concurrent control group, we recommend that you select an approved breast implant. If you choose not to incorporate a concurrent control group, we recommend that you use historical controls and provide the rationale for not using a concurrent control group.

Sample Size
We recommend you base sample size estimates on the precision of safety and effectiveness outcomes or the detection of a clinically meaningful difference from baseline or from a control group, taking into account the lost-to-follow-up rates estimated for 10 years of 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 this precision is within a pre-specified number of percentage points 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 a precision as follows, data on 500 patients would be needed at 10 years post-implantation. If you estimate a hypothetical 40% drop out rate at 10 years, then you should enroll at least 850 patients to achieve 10-year data on 500 patients. This sample size will provide a worst case precision of +/-4%, given a rupture rate of 50%. The precision will improve as the rate moves away from 50%, with a +/-1.9% precision at a rupture rate of 5% or 95%. Pooling of primary augmentation and primary reconstruction cohorts represents the overall best case (i.e. lowest) precision. However, FDA recommends you provide the precision (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 data from primary implantation patients, you should include a proportion of patients presenting for revision. For example, if you estimate approximately 20% of patients present for breast implants due to revision, you should increase the sample size by 20%. Therefore, if you need 850 primary implantation patients, you should enroll approximately 170 revision patients, with the majority of these patients being revision-

augmentation patients. This leads to an overall sample size of approximately 1020 patients.

You should support all marketing claims 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.

Although the sample size example above is based on a worst-case assumption of 40% lost-to-follow-up at 10 years, FDA believes you should provide a minimum of 80% follow-up at each timepoint per patient cohort to have meaningful data to evaluate the safety and effectiveness of your device.

Lost-to-Follow-Up Analyses

High lost-to-follow-up rates may affect FDA's ability to evaluate your PMA. Therefore, we recommend you include a comparison of baseline characteristics between those subjects with complete data and those without to ascertain the presence of any non-respondent bias. We recommend you contact patients who are lost-to-follow-up at the end of the study to determine whether 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 or approval of the PMA because additional clinical data may be necessary.

Data Presentations

The sections below describe the types of safety and effectiveness data that we recommend you provide regarding your Core Study 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 (i.e., asymptomatic rupture) information, are not applicable to saline-filled breast implants.

The majority of the data described below should be reported for the **separate patient cohorts of primary augmentation, primary reconstruction, revision-augmentation, and revision-reconstruction** (i.e., the patient status/indication at study *entry*). Furthermore, you should provide the data on both per patient and per device bases for most of the items below.

8.2 Patient Accounting

We recommend you provide complete patient accounting on a per patient basis for each cohort. You should include the number of patients theoretically due, discontinued because of death or device removal, expected for follow-up, and actually evaluated at each evaluation timepoint. Table 1 below is an example of cumulative patient accounting.

Table 1 - Cumulative Patient Accounting

	Periop	**1 yr**	**2 yr**	**n yr**
Theoretically due[A]	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 and replaced with your devices	0	4	6	
Expected[B]	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%)	

[A]Patients who would have been examined according to date of implantation and follow-up schedules.
[B]Patients who are theoretically due minus the sum of the deaths, removals without replacement, and removals with replacement with different manufacturer's devices.

We also recommend you include the reasons for:

- patients lost to follow-up, as well as any measures to minimize such future events
- patient and physician-initiated discontinuations
- any deaths, including reports from post-mortem examinations.

To limit the potential bias in the safety and effectiveness data, we recommend you provide at least 80% follow-up at each timepoint.

8.3 Demographics and Baseline Characteristics

We recommend you provide the information below regarding demographics and baseline characteristics for each cohort.

Patient Demographics (per patient basis)

- patient age, height, weight, and race
- menstrual status (i.e., last menstrual period (LMP))

Patient Baseline Characteristics (per patient basis)

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

Device Baseline Characteristics (per device basis)

- device surface type (e.g., smooth, textured)
- device type (i.e., single or multi-lumen)
- device style and size
- 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 or delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents, if applicable.

8.4 Safety Assessment - Complications

Complications

The information described below is important in determining the safety of breast implants.[11] Regardless of whether or not the complications may be related to the device, we recommend you provide:

- the incidence, timing, and resolution of all complications, such as rupture, capsular contracture (include Baker Grade), infection, calcification, malposition, extrusion, skin erosion, necrosis, lymphadenopathy, delayed wound healing, breast/chest/axillary mass formation, hematoma, seroma, pain, wrinkling, asymmetry, scar formation, palpability/visibility of the device, iatrogenic injury, etc.

- the incidence, timing, and severity of alterations in nipple or breast sensation

- the incidence, timing, and severity of interference and/or difficulties with lactation, as well as the frequency of attempted lactation without success

- the incidence, timing, and nature of difficulties with pregnancy

- the incidence, timing, and cause of patient deaths (the causes of death should be taken from post-mortem examinations)

- the incidence, timing, and type of new breast cancer diagnosis post-implantation,

[11]Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. [IOM Report] Safety of Silicone Breast Implants; http://www.iom.edu/.

including any mammographic difficulties/interference caused by the device

- the incidence, timing, and extent of new connective tissue disease (CTD) diagnoses, signs, and symptoms.

Cumulative Incidence of Complications
We recommend you provide the cumulative incidence of each complication at each timepoint on both per patient and per device bases for each cohort. This data set should include reoperation and removal with or without replacement.

You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be 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 should be counted once in the numerator if that same complication did not resolve 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 should be counted twice in the numerator.

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

Each capsular contracture grade should be considered a new or different complication and a new (after implantation) diagnosis of breast cancer should be considered a new complication.

Kaplan-Meier Analyses of Complications
We recommend you provide Kaplan-Meier analyses (i.e., 1 minus the complication-free survival rate over time) on both per patient and per device bases for each cohort for each complication, whether or not the complications may be related to the device. The Kaplan-Meier analyses should include reoperation and removal with or without replacement. For capsular contracture, you should present capsular contracture grades II, III, and IV separately, as well as capsular contracture grades III and IV together. For rupture of silicone gel-filled breast implants, see Section 8.5 below for more details.

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

Summary Table of Reoperations, Additional Surgical Procedures, Patients, and Implants
We recommend you provide a table that summarizes the number of reoperations and corresponding number of additional surgical procedures, patients, and implants, per indication, for the Core Study. See the sample table below.

Indication	Number of			
	Reoperations	Additional Surgical Procedures	Patients	Implants
Augmentation				
Reconstruction				
Revision-Augmentation				
Revision-Reconstruction				

Primary Reasons for Reoperation

A reoperation is defined as a single surgery performed on a patient at a given timepoint, irrespective of whether one or two implants are involved. If a patient undergoes another surgery at a later timepoint, it should be counted as a separate reoperation. One or more reasons for a single reoperation may be reported by a surgeon.

If more than one reason for a single reoperation is reported, FDA recommends you determine the primary reason using the following hierarchy:

- rupture/deflation
- infection
- capsular contracture
- necrosis/extrusion
- hematoma/seroma
- delayed wound healing
- breast pain
- implant malposition
- wrinkling
- palpability/visibility
- asymmetry
- ptosis
- scarring
- nipple complications
- device injury/iatrogenic
- breast cancer mass
- biopsy
- patient request for style/size change.

We recommend you provide the cumulative primary reasons for reoperation for each cohort at each timepoint. The denominator should be the total number of reoperations since the initial implantation until that timepoint. Because you are providing primary reasons, the sum of the numerators should equal the denominator.

Primary Reasons for Device Removal
We recommend you provide the cumulative reasons for device removal for each cohort at each timepoint. The denominator should be the total number of devices removed since the initial implantation until that timepoint. If more than one reason for a single removal is reported by the surgeon, then FDA recommends you determine the primary reason using the same hierarchy above used to determine the primary reason for a reoperation. Because you are providing primary reasons, the sum of the numerators should equal the denominator.

Types of Additional Surgical Procedures
Multiple surgical procedures can be performed in a given reoperation. Examples of types of additional surgical procedures include capsulotomy, capsulectomy, device removal followed by replacement, device removal without replacement, saline volume adjustment, reposition of device, drainage of abscess/hematoma/seroma, excision of masses/lymph nodes in ipsilateral axilla or arm of implanted breast, and biopsy/cyst removal.

We recommend you provide the cumulative types of additional surgical procedures for each cohort at each timepoint. The denominator should be the total number of additional surgical procedures since the initial implantation until that timepoint. If more than one type of procedure is reported for a reoperation, you should report all procedures performed.

Cumulative Incidence of Complications after Removal of Study Device With Replacement
As stated above, we recommend you continue to follow patients who have undergone device removal with study device replacement. We recommend you provide the cumulative incidence of individual complications at each timepoint on both per patient and per device bases for each cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint. See the ***Cumulative Incidence of Complications*** section above for more details.

Cumulative Incidence of Complications after Removal of Study Device Without Replacement
As stated above, we recommend you continue to follow patients who have undergone device removal without replacement in order to assess complications that may occur after removal, particularly for those patients who had their device(s) removed due to rupture. We recommend you provide the cumulative incidence of individual complications at each timepoint on both per patient and per device bases for each cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint. See the ***Cumulative Incidence of Complications*** section above for more details.

8.5 Safety Assessment – Rupture

Rupture of Silicone Gel-Filled Breast Implants

FDA believes device rupture is one of the primary safety concerns presented by gel-filled breast implants. When a silicone gel-filled breast implant ruptures, the patient and the physician are often unaware of it (i.e., silent rupture or asymptomatic rupture). The rupture may be intracapsular (when the gel remains within the scar tissue capsule surrounding the implant), extracapsular (when the gel moves outside the capsule but remains within the breast tissue), or involve migrated gel (when the gel moves beyond the breast).

FDA recommends magnetic resonance imaging (MRI) as the current method of choice for detecting silent rupture of silicone gel-filled breast implants. In fact, the sensitivity of physical examination to detect silicone breast implant rupture is 30%[12] compared to 89% for MRI.[13] MRI of the breast should be performed with a dedicated breast coil, with a magnet of at least 1.5 Tesla, and preferably in centers experienced in performing and interpreting this type of examination. The MRI films should be read by both the local radiologist at the center performing the exam and by a radiologist experienced in reading breast implant MRIs (i.e., qualified MRI assessor). The radiologists should be masked to the investigator's judgment of a possible rupture (if applicable) and should each perform an independent assessment of each MRI and rate the presence or absence of rupture as definitive, suspicious/indeterminate, or none/intact.

For devices that are explanted, the final rupture determination should be made at the time of explantation. If explantation is not performed for devices reported as definitive or indeterminate for rupture via MRI, the determination of rupture should be based on the worst case reading by either the qualified MRI assessor or the local radiologist.

FDA recommends that all patients undergo MRI evaluations at 1, 2, 4, 6, 8, and 10 years to assure that patients are adequately monitored for silent rupture consistent with the recommended method and frequency that is included in the labeling for the approved silicone gel-filled breast implants. In addition, this allows you to determine a single rupture rate, for each cohort, for the purposes of patient labeling.[14]

If, because of the mechanical or chemical properties of your device, rupture cannot be visualized using MRI, we recommend you develop an alternative validated method with sensitivity and specificity comparable to that of MRI.

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[12] Hölmich, L.R., et al. 2005a. The diagnosis of silicone breast implant rupture. Clinical findings compared to findings at MRI. Ann Plast Surg 54 (6): 583-9.

[13] Hölmich, L.R., et al. 2005b. The diagnosis of breast implant rupture: MRI findings compared to findings at explantation. 2005. Eur J. Radiol. 53: 213-25.

[14] This is not the case with past Core Study designs that involved MRI and non-MRI cohorts because FDA believed those cohorts should not be statistically combined.

To characterize rupture, we recommend you provide:

- the rupture rate over the duration of the Core Study via prospective, sequential screening of the study population using diagnostic radiographic or other techniques of comparable sensitivity and specificity (some of the Core Study data may be premarket and some may be postapproval)

- the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel for all patients with symptomatic or silent ruptured devices

- a detailed description of the local and systemic health consequences for all patients with symptomatic or silent ruptured devices, including the severity of these health consequences and the clinical course of these patients. Systemic health consequences can include the results of connective tissue disease (CTD) screening.

In addition, we recommend you provide the incidence, prevalence, and Kaplan-Meier rates for each of the following rupture events:

- MRI diagnosis of definitive or indeterminate rupture, regardless of confirmation with removal. If there is disagreement between the MRI readings of the qualified MRI assessor and the local radiologist, then the worst case reading from either should be utilized in the silent rupture rate

- rupture noted at removal, regardless of MRI diagnosis

- rupture noted during the retrieval study, if performed and applicable

- overall rupture rate based on rupture data from any of the sources from the 3 bullets above.

For each device suspected of rupture or reported as ruptured, we recommend you provide a summary of the dates and results of all diagnostic procedures performed related to rupture. We also recommend you provide the actual reports of these diagnostic procedures (e.g., MRI reports, mammogram reports) and provide the surgical explant reports for devices removed with or without replacement. In addition, we recommend you provide the final status of each device suspected of rupture or where rupture is confirmed.

Rupture of Alternative Breast Implants

Depending on the filler of your alternative breast implants, FDA may recommend you provide rupture information similar to that described above for silicone gel-filled breast implants.

8.6 Safety Assessment - Connective Tissue Diseases (CTDs)

FDA recognizes that much has been learned over the last decade about CTDs, including data and analysis from the 1999 Institute of Medicine (IOM) Report on the Safety of Silicone Breast Implants.[15] In addition, we recognize that the Core Study is not designed to examine a potential association between breast implants and the development of CTDs. We do recommend, however, that you collect CTD information as part of the overall safety assessment on your device, as well as to provide complete information to patients who may consider getting breast implants.

FDA recommends you conduct the CTD evaluations on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. If indicated, patients should have a follow-up evaluation(s) by a rheumatologist or other appropriate specialist with collection of serological information (e.g., anti-nuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), immunoglobulin levels, c-reactive protein (CRP), anticardiolipin antibodies (both IgG and IgM), evaluation for monoclonal proteins, complement levels).

Because you should refer patients reporting signs and symptoms that were not present at baseline to the appropriate specialist for evaluation, please provide the criteria (i.e., number and types of responses) for referral to a rheumatologist or other specialist. You should also report the proportion of patients who were referred to specialists based on these evaluations.

CTD Diagnoses

CTD diagnoses include:

- 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 syndrome, morphea, carpal tunnel syndrome, multiple sclerosis-like syndrome, multiple myeloma-like syndrome, chronic fatigue syndrome, and fibromyalgia.

We recommend you provide the following on a per patient basis for each cohort:

- 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 and describe how these values were obtained. The denominator should be the number of patients at that timepoint.

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[15] Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. [IOM Report]; http://www.iom.edu/.

CTD Sign/Symptom Categories

A sign/symptom category is an anatomical or body function area (e.g., skin, muscle, joint, gastrointestinal, respiratory, neurological, general). For example:

- skin includes alopecia, facial rash, pruritis, and echymoses
- muscle includes myalgias, muscle weakness, and elevated CRP
- joint includes arthralgia, arthritis, and morning stiffness
- neurological includes cognitive dysfunction, memory problems, peripheral neuropathy, and multiple sclerosis-like symptoms
- general includes fatigue, generalized pain, fever, and depression.

We recommend you provide the following data on a per patient basis for each cohort:

- Kaplan-Meier analysis for each symptom category
- Kaplan-Meier analysis describing patients who are free from one or more positive symptoms
- the cumulative incidence of at least one CTD sign/symptom category at each timepoint. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients at that timepoint.

Individual CTD Signs and Symptoms

Examples of individual CTD signs and symptoms include hair loss, facial rash, photosensitivity, dry eyes, dry mouth, arthralgias, myalgias, neuralgias, difficulty swallowing, morning stiffness that lasts more than 30 minutes, ocular inflammation/retinitis/optic neuritis, muscle weakness, joint swelling for more than 6 weeks, pleurisy, respiratory difficulty, skin rash, lymphadenopathy, cognitive dysfunction, fatigue, paresthesia, dizziness, abnormal bruising or bleeding, purpura, unexplained fever, urticaria, telangiectasia, and petechiae.

We recommend you provide the following data on a per patient basis for each cohort:

- the cumulative incidence of each individual CTD sign and symptom at each timepoint. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients at that timepoint
- the status of device rupture, reported complications, and patient satisfaction for patients reporting CTD signs and symptoms that were not present before breast implantation

- a comparison of the incidence and types of new CTD signs and symptoms reported with information from the published literature or other comparable sources (e.g., data from patients with other types of devices, data from patients seeking other types of cosmetic surgery).

8.7 Safety Assessment - Mammography Data

For patients who undergo screening mammography during the study, we recommend you provide separate analyses for mammographic suspicion for tumor:

- regardless of biopsy results
- with a biopsy positive for malignant 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 per patient and per device bases for each cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint

- the cumulative incidence at each timepoint on both per patient and per device bases for each cohort. You should provide the numerator and denominator used and describe how these values were obtained. The denominator should be the number of patients or devices at that timepoint

- a comparison of the data to that reported in the literature for aged-matched cohorts.

8.8 Effectiveness Assessment

Patient Reported Outcomes (PROs)

We recommend you provide the results from PRO assessments to assess the beneficial impact of the device. These are the same assessments that were previously referred to by FDA as health related quality of life assessments. These assessments should include, but need not be limited to:

- a measure of self esteem (e.g., Rosenberg Self Esteem Scale[16] or Tennessee Self-Concept Scale[17])
- a measure of body image (e.g., Body Esteem Scale[18])

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[16] Rosenberg, M. 1989. *Society and the Adolescent Self-Image*. Revised edition. Middletown, CT: Wesleyan University Press.

[17] Fitts, W. Tennessee Self-Concept Scale: Manual. Western Psychological Services, Los Angeles, CA, July 1989.

[18] Franzoi, S and Shields, S. (1984). The Body-Esteem Scale: Multidimensional structure and sex differences in a college population. *Journal of Personality Assessment*, *48*, 173-178.

- a measure of general health outcome (e.g., SF-36 Status Survey,[19] Medical Outcomes Study (MOS) 20-Item Health Survey[20]).

FDA recommends you conduct PRO assessments on all patients at the preoperative timepoint and at the 1, 2, 4, 6, 8, and 10-year postoperative timepoints. For reconstruction patients, you should describe the timing of administration of these instruments (delayed or immediately following reconstruction).

We recommend you provide the mean (± standard deviation) change in each validated PRO measure (preoperative to each visit). You should report these results on a per patient basis for each cohort. The denominator should be the number of patients evaluated at each visit interval. FDA also recommends that you compare your results to published normative data for those PROs for which these data exist (e.g., SF-36).

Satisfaction

We also recommend you provide data on patient satisfaction. Patient-reported satisfaction measures should incorporate satisfaction based on:

- preoperative expectations
- the initial surgical procedure
- any adjunctive surgical and medical procedures
- any complications
- device *removal*, regardless of whether the device was replaced
- whether the expected benefits of the devices have been met
- whether the patient would have the surgery over again.

For those patients reporting dissatisfaction following breast implantation, we recommend you provide the following information:

- detailed reason for dissatisfaction
- presence, severity, status (i.e., resolved or not resolved), and method of resolution of any complications
- reports of CTD diagnoses, signs, and symptoms.

Anatomical Effect

We recommend you provide data on the anatomical effect of the device for augmentation and augmentation-revision cohorts. This may be accomplished by comparing matched analyses of before and after bra and cup sizes, chest circumference, symmetry, or other

[19] Ware J, et al. SF-36 Health Survey Manual and Interpretation Guide. The Health Institute, New England Medical Center, Boston, MA 1993.

[20] Stewart A., et al. The MOS Short-Form General Health Survey: Reliability and validity in a patient population. Medical Care 1988; 26: 724-735.

standardized measurements. For example, we recommend you provide the following on a per patient basis:

- frequency distribution of bra cup size at baseline, end of study, and change from baseline
- mean (± standard deviation) chest circumferences at baseline, end of the study, and change from baseline.

8.9 Other Statistical Analyses

Sample Size Rationale

We recommend you provide the statistical rationale for why the sample size is adequate to evaluate the device. This should include:

- identification of effect criteria (i.e., clinically significant difference in the response variables to be detected)
- statistical error tolerances of alpha and beta (as applicable)
- desired precision for rate estimates (e.g., defined as ½ width of confidence interval)
- 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.

Pooling Analyses

We recommend you provide the statistical rationale for pooling across:

- investigational sites
- demographic and baseline characteristics.

Logistic Regression Analyses of Each Safety and Effectiveness Outcome

To determine which variables are associated with each safety and effectiveness outcome, we recommend you provide logistic regression analyses, where appropriate, on a per device basis for each cohort using, but not necessarily limited to, the following static covariates:

- patient age
- indication for use (i.e., augmentation, reconstruction, revision-augmentation, or revision-reconstruction)
- device surface type (i.e., smooth or textured)
- device type (i.e., single or multi-lumen)
- device size
- valve type (e.g., leaf, diaphragm)
- surgical incision site (e.g., periareolar, inframammary fold, axillary)

- incision size
- device placement (e.g., retromuscular, subglandular)
- timing of reconstruction (i.e., immediate or delayed)
- use and type of surgical pocket irrigation
- use and type of intraluminal agents.

Cox Proportional Hazards Regression Analyses of Rupture/Deflation
To determine which variables are associated with rupture/deflation, we recommend you provide Cox regression analyses of rupture/deflation on a per patient basis for each cohort using the static covariates above, as well as time-dependent covariates (e.g., infection, capsular contracture). The coefficient estimates should be the relative risks (hazard ratios) of rupture/deflation based on transition to a complication. An advantage of this approach is that rupture/deflation is 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.

Generalized Estimating Equations (GEE) Analyses of CTDs
To analyze whether any increases in the signs and symptoms of CTDs were due to the implant or due to the increased age of the patient, we recommend that you provide GEE analyses on a per patient basis for each cohort, using age as a covariate.

9. Other Clinical Data

9.1 Supplemental Clinical Information to Address Rupture

This section pertains only to silicone gel-filled and alternative breast implants.

Silicone Gel-Filled Breast Implants
Because of its limited sample size, we believe the Core Study may not fully address concerns about device rupture. Using other sources of information, such as other U.S. or European retrospective or prospective studies or the literature, we recommend you provide the following additional clinical information on your device:

- any available long-term rupture rate data, ideally collected via prospective, sequential screening of the study population using diagnostic radiographic or other techniques of comparable sensitivity and specificity
- the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel
- a detailed description of the local and systemic health consequences for all patients with ruptured devices (both symptomatic and silent rupture patients), including the severity of the local health consequences and the clinical course of these patients
- the incidence, prevalence, and timing of silent ruptures that progress to symptomatic ruptures

- the incidence, prevalence, and timing of intracapsular ruptures that progress to extracapsular ruptures.

Alternative Breast Implants
Depending on the design or materials of your alternative breast implant, FDA may recommend supplemental clinical information similar to that described above for silicone gel-filled breast implants.

9.2 Supplemental Literature Information

Because of the limited sample size of the Core Study, we recommend you provide a current review of the literature on breast implants for the topics below. The topics include:

- cancer (both breast and non-breast)
- benign breast disease
- CTD diagnoses, signs, and symptoms, including fibromyalgia
- interference of device with mammographic detection of tumors or rupture
- neurological disease
- ability to lactate
- offspring issues (safety of milk for breastfeeding and 2nd generation effects)
- potential systemic health consequences of extracapsular and migrated gel rupture
- potential health consequences of gel bleed
- depression, anxiety, and suicide.

We recommend you provide a thorough search of current medical literature on breast implants to address the range of clinical experience with each of the topics bulleted above as they relate to the specific type of device (i.e., silicone gel-filled, saline-filled, or alternative), as well as the criteria and method for selecting the literature. We recommend you provide copies of the literature references and develop a table that summarizes the information.

We recommend you provide literature information specific to the subject breast implant type. However, if no device type-specific information is available, you should provide pooled data (e.g., silicone gel and saline data) from the literature.

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

10. Labeling

10.1 General Information

General labeling requirements for medical devices are described in 21 CFR Part 801. Additional labeling requirements for IDE submissions are found in 21 CFR §§ 812.5 and 812.20(b)(10). Additional labeling requirements for PMA submissions are found in 21 CFR § 814.20(b)(10). The IDE and PMA regulations require that you provide copies of all labeling for your device(s). For additional information on labeling, please see the guidance document, "**Device Labeling Guidance #G91-1,** http://www.fda.gov/cdrh/g91-1.html.

Below is a description of the physician labeling, patient labeling, and patient device card, which we recommend that you provide for your device, when submitting an IDE or a PMA for a breast implant.

10.2 Physician Labeling

We recommend you provide physician labeling (i.e., package insert) for a breast implant PMA that includes the following types of information:

- device name, styles, and brief device description
- name and address of manufacturer, packer, or distributor
- "Sterile," "Do not resterilize," and "Single use only" notations (or similar wording)
- indications for use
- any relevant contraindications (including surgical procedures which are contraindicated due to interference with device integrity or performance)
- any relevant warnings, including, but not necessarily limited to:
    - a warning against closed capsulotomy because it has been shown to potentially result in device rupture
    - a warning 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
- any relevant precautions
- list of potential complications[21]
- preoperative patient procedures (e.g., prophylactic antibiotics), operating room procedures (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)

[21] Refer to the "**FDA Breast Implant Consumer Handbook**" for additional information regarding potential complications. This handbook is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

- intraoperative test procedures to ensure device integrity and proper placement (if necessary)
- instructions for postoperative patient care, including how to monitor device integrity and placement
- instruction on how to minimize failure related to surgical procedure based on modes/causes of rupture studies
- appropriate clinical study safety and effectiveness results
- appropriate preclinical study results, including modes/causes of rupture and gel bleed results
- literature information as per Section 9.2 above
- recommendations for method(s) and frequency of screening for rupture
- clinical management of suspicious and confirmed rupture
- recommendation for implant removal if rupture is detected.

The IDE physician labeling should include all elements identified in the bullets above except for those involving specific clinical results. In addition, the labeling must include the following statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." (21 CFR § 812.5).

You should make the physician labeling available to the patient before the surgery, upon request, whether the request comes directly from the patient or through the physician or surgeon.

10.3 Patient Labeling

The purpose of the patient labeling is to provide a patient with sufficient information (e.g., realistic expectations of the benefits and risks) so that she may make an informed decision as to whether or not to receive breast implants.

For a PMA, patient labeling is often referred to as a patient brochure, a patient booklet, or patient informed decision labeling. We recommend the patient labeling in your PMA include the following types of information:

- device name, styles, and brief device description
- indications for use
- relevant contraindications, warnings, and precautions
- potential complications, including possible methods of resolving them
- postoperative care instructions (e.g., what to expect after surgery, symptoms to tell doctor about immediately, length of recovery, physical limitations, how to monitor her breast)
- factors to consider in deciding whether or not to get breast implants (e.g., may not be

lifetime device or one-time surgery, many of the changes to breasts following implantation are irreversible, breast implants may affect the ability to breast feed, routine screening mammography may be more difficult, there may be health insurance coverage issues)

- other factors to consider (e.g., choosing a surgeon, device size and shape, surface texturing, palpability, device placement, incision sites)
- warranty information
- toll-free number for questions/information
- appropriate clinical study safety and effectiveness results
- appropriate preclinical study results, including gel bleed results
- literature information as per Section 9.2 above
- recommendations for method(s) and frequency of screening for rupture
- clinical management of suspicious and confirmed rupture
- recommendation for implant removal if rupture is detected.

For an IDE study, informed consent must be documented (21 CFR § 50.27). The basic elements of informed consent are described in 21 CFR § 50.25, and include some of the information in the bullets above.

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 surgical patient.

PMA patient labeling and the IDE informed consent document should not exceed the reading comprehension level that is easily 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, we recommend you refer to "**Guidance on Medical Device Patient Labeling**" at http://www.fda.gov/cdrh/ohip/guidance/1128.pdf and information regarding plain language at http://www.plainlanguage.gov.

We also recommend you refer to the FDA breast implant consumer handbook entitled, "**FDA Breast Implant Consumer Handbook**" for additional information regarding potential complications, factors to consider, surgical alternatives, etc. This handbook is available through FDA's breast implant website at http://www.fda.gov/cdrh/breastimplants/.

10.4 Patient Device Card

We recommend you provide patient device cards as part of the informed consent process for your IDE study and as part of the patient labeling for your PMA approved device. 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. Regardless of the name used, its purpose is to provide the patient with specific information about her device(s). The

device card should include, but need not be limited to, the device's style, size, and serial or lot number. Typically, multiple device labels or stickers are provided with the device card that includes this information. If that is the case, at the time of surgery, one label or sticker should be placed in the patient's records and one label/sticker should be placed on the device card. We recommend the physician or surgeon give the device card to the patient immediately following surgery.

11. Postapproval Requirements

As a condition of approval of your PMA, or in connection with the approval, FDA may require you to conduct postapproval studies, to track your device, or to comply with restrictions relating to the sale, distribution, or use of your device (FDCA §§ 515(d)(1)(B)(ii), 519(e), 520(e), and 522 (21 U.S.C. §§ 360e(d)(1)(B)(ii), 360i(e), 360j(e), & 360l), and 21 CFR Part 814, Subpart E.). Specific postapproval commitments for your PMA will be determined at the time of PMA approval; however, these requirements could include:

- continued follow-up of your Core Study patients. In determining whether to require annual mail-in questionnaires or annual physician follow-up visits, FDA will consider the specific device and the available premarket data
- a patient registry or additional postapproval study (other than postapproval Core Study above) to collect additional postapproval data
- additional studies to address the modes and causes of failure
- an education and certification program to train physicians and surgeons with regard to proper surgical technique, patient selection, patient monitoring, and management of complications to obtain access to your device
- focus group study to improve the patient labeling
- a formal informed decision process that assures that a woman has been provided the patient labeling with adequate time to read it prior to surgery and that documents that she has an adequate understanding of the risks and follow-up recommendations associated with your device
- labeling updates on a regular interval to reflect any appropriate findings from postapproval studies.

FDA also intends to require mandatory tracking upon approval of a silicone gel-filled breast implant PMA. Mandatory tracking is not specified as a condition of PMA approval under the PMA regulations. Instead, FDA issues tracking orders pursuant to FDCA § 519(e) (21 U.S.C. § 360i) and 21 CFR Part 821.