FDA SUMMARY PANEL MEMORANDUM

TO: **General and Plastic Surgery Devices Advisory Panel Members**

FROM: FDA's Mentor PMA Review Team

DATE: March 2, 2005

SUBJ: P030053 - Mentor Corporation
Silicone Gel-Filled Breast Implants

In December 2003, an original PMA submission (P030053) was received from Mentor. FDA issued a major deficiency letter on 4/14/04. In August 2004, Mentor provided responses to the issues raised in their major deficiency letter. Because this PMA has not been previously presented to an Advisory Panel, this memo includes a review of all primary sections of the PMA, which incorporates a discussion of their August 2004 responses.

The primary sections of a PMA are the (1) device description, (2) preclinical data, (3) clinical data, (4) postapproval plans, (5) device reports, and (6) labeling. Below is a brief description of each of these sections.

1. **Device description** section provides a brief description of the device and identifies the styles under PMA review.

2. **Preclinical** sections include chemistry, toxicology, modes and causes of rupture, fatigue, gel cohesion, gel bleed, and shelf life.

3. **Clinical** sections include:

   - Core Study Clinical Data - The Core Study is a 10-year prospective clinical study that collects safety (local complications) and effectiveness data on Mentor's silicone gel-filled breast implants - Smooth Moderate Profile and Siltex Moderate Profile for augmentation, reconstruction, and revision indications. The date of database closure was 7/15/04. The Core Study does not include the Smooth or Siltex Moderate Plus Profile or High Profile implant styles for which Mentor is seeking approval in this PMA. This is the primary clinical data set for this PMA.

   - Rupture Rate and Health Consequences – This section summarizes information from various clinical sources to address this FDA's deficiencies pertaining to implant rupture and health consequences of rupture.

   - Adjunct Study Clinical Data - The Adjunct Study is an ongoing 5-year prospective clinical study that collects safety (local complications only) data on Mentor's Smooth and Siltex Moderate Profile and High Profile implant styles for reconstruction and revision

indications. The Adjunct Study was established to make silicone gel-filled breast implants available for reconstruction and revision patients as per FDA's 1992 determination that there was a public health need for these patients to receive silicone gel breast implants.

- Supplemental Literature Information – This section addresses published literature on various safety topics. The literature is not specific to Mentor's implants.

4. **Postapproval plans** include Mentor's proposals for postapproval commitments, should the PMA be approved. The topics include a Core postapproval study, a patient registry, a focus group study, and physician training/education.

5. **Device reports** include a general review of FDA's MedWatch information and of Mentor's complaint database.

6. **Labeling** sections include an overview of the proposed labeling for the device.

The purpose of this Summary Panel Memorandum is to provide you with a summary review of 6 PMA sections above. Manufacturing information, another primary element of a PMA, will not be discussed in this Summary Panel Memorandum.

For additional information regarding FDA's recommendations for the types of preclinical and clinical data to submit in support of a breast implant PMA, please refer to "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" dated 1/13/04 and available at http://www.fda.gov/cdrh/ode/guidance/1239.pdf.

TABLE OF CONTENTS

A. DEVICE DESCRIPTION

The Mentor Silicone-Gel Filled Breast Implants are available in smooth and textured (Siltex) surfaces with round shapes. The minimum shell thickness is -------- for smooth devices and -------- for Siltex devices. All styles are single lumen devices. All implants are dry heat sterilized.

The table below summarizes the implants included in this PMA application.

Style	Shape, Profile	Shell Surface	Volume (cc)
7000	Round, Moderate Profile	Smooth	100-800
7000	Round, Moderate Profile	Siltex	100-800
4000	Round, High Profile	Smooth	125-800
4000	Round, High Profile	Siltex	125-800
8000	Round, Moderate Plus	Smooth	100-800
8000	Round, Moderate Plus	Siltex	100-800

Mentor distinguishes their devices by profile and use as follows:

- Moderate Profile Gel - for patients who have a wider chest wall (most commonly used product line)
- Moderate Plus Gel - for patients who require more projection and a slightly more narrow base width
- High Profile Gel – for patients with narrow chest wall who are seeking more projection, which is relevant in reconstruction when trying to match a non-reconstructed breast.

The Mentor Silicone Gel-Filled Breast Implant is composed of silicone gel encased in a silicone elastomer envelope (shell). The shell contains a patch, made from silicone elastomer, which covers the hole in the posterior shell that results when the shell is removed from the mandrel during manufacture. During manufacture, the gel is injected through the patch/reinforcement dot and then the fill hole is sealed using a small amount of dispersion coating. The device then undergoes final curing. Thus, the primary components of the subject implants are the shell, patch, silicone gel filler, and dispersion coating. Below is a detailed description of each of the primary components, including the materials.

The **shell** is manufactured from Dimethyl Silicone Elastomer Dispersion (base layer) which forms a sandwich on either side of ---------- Silicone Dispersion that acts as a barrier layer to minimize the rate of low molecular weight silicones diffusion. Both the dimethyl layer (base layer) and ---------- (barrier) layer are made by heat-cured platinum-catalyzed curing process. Amorphous fumed silica is added to the formulation to significantly increase the physical properties of the elastomer.

For Siltex devices, the shell texturing process is as follows. ---------- ---------- ---------- ---------- ---------- -- ---------- ---------- ----------

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The **patch** can be made from two different silicone elastomers. The uncured polysiloxane elastomer is placed on the inside of the shell, pressed together in a vulcanization press, and then subjected to an elevated temperature in the vulcanization press (heat-cured in presence of platinum). The patch on Siltex devices is also textured, as described above for the shell. For all device patches, a reinforcement dot, which is a small round disc of silicone elastomer, is pressed onto the patch and heat-cured.

The **silicone gel** is lightly cross-linked, platinum-catalyzed dimethyl siloxane gel (polydimethyl methlyvinylsiloxane and polydimethyl methylhydrogensiloxane) that is injected into the device through the reinforcement dot and then heat-cured. The gel formulation contains ---------- ----- ----------) and does not participate in the curing reaction. The oil most likely intercalates the gel and provides fluid characteristics to the gel.

The **dispersion coating** consists of 1 to 2 drops of room temperature vulcanized (RTV) uncured silicone which consists of amorphous silica reinforcing filler, dimethyl silanol terminated poly (dimethyl siloxane) polymer, a tin catalyst, and ---------- ---------- -------- as the crosslinker. The dispersion coating is placed onto the reinforcement dot after gel filling to seal the fill hole. The device is then heat-cured.

As additional information, the following are all design changes and significant manufacturing process changes made to Mentor's gel-filled device since 1991. The changes include:

- ------ elastomer introduced in 1993 to replace --- ---------- materials
- ---------- silicone gel introduced in 1995 to replace ----- ---------- ------ -
- minimum shell thickness increased by -------- in 1998
- f-------layer added to shell in 1998 for more consistent shell thickness and meet minimum shell thickness
- -------- dispersion and gel (alternate vendor) introduced in 1999
- gel fill amount changed in 2001 to meet ASTM and ISO requirements
- changed ---------- for cured HTV dispersions in 2003
- minimum thickness increased by -------- for moderate and high profile gel shells in 2003.

B. CHEMISTRY DATA

Below is a review of the chemistry data in this PMA application.

1. Extent of Crosslinking

Shell - Three Siltex Round Moderate Profile Gel-Filled (100 cc) devices were subjected to additional thermal cure step consisting of 240 minutes at 164°C. The device shells were then subjected to exhaustive extraction conditions ----------before and after the additional thermal cure step. The molar crosslink density (ρ_c), and crosslink chain density ($\rho_c N_{AV}$) were calculated to be 1.31E-4 mol/cm^3 and 7.90E+19 chain/cm^3, respectively, by the Sol Fraction Method (equilibrium swell ratio). The three devices tested showed similar results, indicating the crosslink density is the same across lots. The results also demonstrated that the curing reaction was complete because there was no change in these results after additional cure step.

Gel - The experiments were repeated with the gel component under the same conditions as described for the shell and the molar crosslink density (ρ_c), and Crosslink Chain Density ($\rho_c N_{AV}$) were calculated to be 1.46E-6 mol/cm^3 and 8.81E+17 chain/cm^3, respectively. The three devices tested showed similar results, indicating the crosslink density is the same across lots.

2. Volatiles

Shell - Shell samples were cut into 2mm x 2mm pieces, and the volatiles were analyzed by headspace purge/trap connector coupled with GC/MS (gas chromatography – mass spectrometry). The results are presented in the table below. Shells from unfilled devices (not exposed to gel) and from fill-d devices (exposed to gel) were tested. The shells not exposed to gel contained ----- µg/g of volatiles, of which the notable compounds were ---------- - ---------- ---------- --------- ---------- -

The shells exposed to gel contained ----- µg/g of volatiles.

Gel - The analysis on the gel was performed in the same way as for the shell component. The gel filler contained --- µg/g of volatiles. The notable compounds were D4 (--- ppm), D5 (--- ppm), and undecane (--- ppm).

Whole Device - The analysis on the whole device was based upon the weight averaged calculation of the analyses performed on the individual shell and gel components.

The results are presented in the table below.

Compound	Shells Not Exposed to Gel (ppm)	Shell Exposed to Gel (ppm)	Gel Filler (ppm)	Whole Device (ppm)
----------	----------	----------	-----	-----
----------	-------	-----	-----	-----
----------	------	-----	-----	-----
----------	-----	-----	----------	-----
----------	----------	-----	----	-----
----------	-----	----------	----	----------
----------	--------	--------	-----	-----
----------	----------	------	----------	----------
----------	------	-----	----	-----

Compound	Shells Not Exposed ----- el (ppm)	Shell Exposed to --- l (ppm)	Gel Filler --------	Whole Device --------
[redacted]				
Total Volatiles	--------	--------	------	-----

3. Extractables

Siltex Round Moderate Profile Gel-Filled (100cc) devices were used for this testing. The components were extracted (exhaustive) with different solvents. Methylene chloride was eventually chosen to be the best solvent for extraction. The residue obtained was subjected to different analyses described below.

Gravimetric Analysis

Shells not exposed to gel gave ------- by weight of extractable residue. Shells exposed to gel gave --------- by weight of extractable residue. The gel gave --------- by weight of extractable residue. The whole device gave --------- by weight of extractable residue.

FTIR Analysis

Fourier Transform Infra Red (FTIR) spectroscopic analyses on the shell and the gel, as well as the extractable residues, showed that the extractable materials are polysiloxanes. Mentor stated that no ----- - groups were detected because of their low concentrations.

Gel Permeation Chromatography

With regard to the shell exposed to gel, the extrac---- ---esidue on GPC analysis gave two peaks: (1) a larger molecular weight (M_w) peak at about [redacted] Daltons for polydimenthylsiloxane and (2) a small molecular weight pea- that contained low molecular weight---------- The larger molecular weight peak represents a methyl substitu ted polysiloxane polymer with a polydispersity of ---- Its origin was determined to be from the gel.

With regard to the shell not exposed to gel, the extractable residue contained----- polymer, oligomer and monomeric species with a molecular weight (M_w) range [redacted] Daltons. The -------- substituted siloxanes ranged in concentration from [redacted] ppm. The extract also yielded two peaks of ---- ----- siloxane species, one with a molecular weight of [redacted] Daltons

and a second one with a molecular weight of ----- Daltons. The high molecular weight species represented less than ----- of the total peak area.

With regard to the gel, the extractable residue on GPC analysis gave only one peak with a polydispersity of --- (M_w = 53900 & M_w = 22,300; M_w / M_w = -----

Semi-Volatile Qualitative and Quantitative Analyses

With regards to the shell extractables, a part of the residue from the extraction of the finished device shell was subjected to GC/MS analyses. The analysis showed that it contained no detectable amounts of D4 and, at most, a total of --- ppm of D5 – D10. It also contained a total of ≈---- ppm of linear dimethyl siloxanes. The total amount of vinyl-modified cyclic siloxanes were <--- ppm, and the total amount of ---------- cyclic siloxanes was <--- ppm.

With regards to the gel extractables, extraction residue from the filler on GC/MS analysis was shown to contain --- ppm of D4 and approximately ------ ppm of D4-D21. Linear dimethylsiloxanes were determined to be ---- ppm. Vinyl modified siloxanes were ---- ppm, while no ---------- cyclic siloxanes were detected in the gel.

The GC/MS analyses (qualitative and quantitative) results for the semi-volatiles, including that for the whole device, are listed in the table below.

Compound	Shell Not Exposed to Gel (µg/g)	Gel Filler (µg/g)	Shell Exposed to Gel (µg/g)	Whole Device (µg/g)
Cyclic Dimethyl Siloxanes				
D_4	----	---	----------	----------
D_5	----	---	-----	-----
D_6	----	---	-----	-----
D_7	----	---	-----	-----
D_8	-----	---	-----	-----
D_9	-----	----------	----------	----------
D_{10}	----------	-----	----------	--------
D_{11}	------	-----	------	--------
D_{12}	-----	-----	-----	------
D_{13}	----------	----------	----------	----------
D_{14}	------	------	----------	--------
D_{15}	------	------	------	----------
D_{16}	------	------	------	------
D_{17}	------	------	------	------
D_{18}	----------	------	------	------
D_{19}	--------	------	------	------
D_{20}	--------	------	------	------
D_{21}	--------	------	------	------
Linear Dimethyl Siloxanes				
MD_7M	----	-----	----	-----
MD_8M	----	----------	----	----------
MD_9M	----	---	----	---
$MD_{10}M$	----	----------	----------	----------
$MD_{11}M$	----	-----	------	------
$MD_{12}M$	----	-----	----------	----------

Compound	Shell Not Exposed to Gel (µg/g)	Gel Filler (µg/g)	Shell Exposed to Gel (µg/g)	Whole Device (µg/g)
$MD_{13}M$	----	-----	-----	-----
$MD_{14}M$	----	-----	-----	-----
$MD_{15}M$	----	-----	-----	-----
$MD_{16}M$	----	-----	-----	-----
$MD_{17}M$	----	-----	-----	-----
Vinyl-Modified Cyclic Dimethylsiloxanes				
$D^{vi}D_{14}$	----	-----	-----	---
$D^{vi}D_{15}$	----	-----	-----	-----
$D^{vi}D_{16}$	----	-----	------	------
$D^{vi}D_{17}$	----	-----	-----	-----
$D^{vi}D_{18}$	----	-----	-----	-----
$D^{vi}D_{19}$	----	-----	-----	-----
[redacted]				
[redacted]	-----	----	----	----
[redacted]	-----	----	----	----
[redacted]	-----	----	-----	----
[redacted]	-----	----	-----	----
[redacted]	-----	-----	-----	------
[redacted]	-----	-----	-----	------
[redacted]	-----	-----	-----	-----
[redacted]	-----	----	-----	-----
[redacted]	-----	----	-----	-----
[redacted]	-----	----	-----	-----
[redacted]	-----	----	----	----
[redacted]	-----	----	----	----
Miscellaneous Siloxanes				
Siloxane	----	---	---	---
Residues of Solvents and Plasticizers				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (µg/g)	---------	---------	---------	---------

ND = Not Detected, S/N <3.0
NA = Not Applicable. At least one of the replicates has a ND value.
vi = vinyl; -- --- -----
Data preceded with a "<" symbol meaning a less than method detection limit value was measured in the sample or individual component

Mentor stated that the concentrations of the oligosiloxanes present in the device are well below the No Observed Adverse Effect Level (NOAEL). They based their argument on extrapolation of the available toxicology data on D4 and D5.

Mentor further stated that aqueous solubility, toxicity, and biological activity of permethylated cyclic siloxanes decrease with increasing size. An article by Varaprath, S. et al[1] is quoted which demonstrates that the aqueous solubility of D5 is 4.2-fold lower that of D4, while the aqueous solubility of D6 is 4.0-fold lower than that of D5. The NOAEL for D5 is 14-fold higher than that for D4. In an adjuvancy study by Klykken et al.[2], the observed activity decreased significantly in

the series D4>D5>D6>D7. Based on the hypothesis put forward by Klykken, et al., Mentor calculated a risk analysis that showed that the worst-case exposure of these oligosiloxanes was significantly lower than the NOAEL.

4. Heavy Metal Analysis

Both the shell and the gel components were extracted with aqueous (buffer) and organic solvents in accordance with EPA Method 1311 "Toxicity Characteristic Leaching Procedure." For aqueous buffer, the mass/volume ratio was 1/20 for 120 hours, and the temperature was 37°C. For organic solvents (methylene chloride) extraction was done at room temperature, at a ratio of 1/20, and for 20 hours for shell and 30 hours for gel. The components were analyzed by Inductively Coupled Plasma/Mass spectroscopy) (ICPM) for numerous metals. The metal concentrations obtained from the extracted residues are listed in the table below.

Metal Name	Concentration (ppm)
Antimony	------
Arsenic	------
Barium	------
Beryllium	------
Cadmium	------
Chromium	------
Cobalt	------
Copper	------
Lead	------
Magnesium	------
Mercury	------
Molybdenum	------
Nickel	------
Platinum	------
Selenium	------
Silver	------
Tin	------
Titanium	------
Vanadium	------
Zinc	------

Mentor's studies on the nature of the (1) platinum catalysts, (2) the active platinum species during hydrosilation reaction, and (3) the platinum-containing end products after hydrosilation concluded that Platinum after the hydrosilation reaction will not be present in any oxidation state other than zero oxidation state.

5. Other

X-Ray diffraction studies on the elastomer shell confirmed that the silica used as reinforcing filler material is in the amorphous form.

C. TOXICOLOGY DATA

Below is a review of the toxicology data.

Pharmacokinetics

Mentor cited a number of experiments in which ^{14}C-labeled polydimethylsiloxanes were injected subcutaneously in animals. Most of the radioactivity (94-99.97%) remained at the injection sites. In one experiment, less than 0.02% was found to have migrated to different tissues. Raposo do Amaral, et al.[3] injected rats with 2ml of silicone gel at 2 different sites and followed the animals for various time periods up to 450 days. Silicone was not detected in the heart spleen, liver, stomach, or gonads, but it could be detected locally surrounding the tissue capsules at the implantation sites. No silicone was found in the regional lymph nodes.

Swanson, et al.[4] evaluated 3 dogs ten years after implantation with silicone elastomer joint implants. At the postmortem examinations, there was little evidence of migration. Particles were found around the joints, but no particles were found at distant sites except for a few particles in the axillary lymph nodes. Swanson also reported on the autopsy of a rheumatoid patient who had silicone implants in hands, radial heads, and feet beginning 12 years before death. Silicone particles were found in giant cells in the synovium with minimal inflammatory cells, but no focal necrosis. Some silicone was also found in giant cells in an axillary node.

With regard to the migration of low molecular weight mixtures of the cyclic siloxanes (e.g., D4, D5, D6), Kala, et al.[5] injected a distillate of cyclic siloxanes in the suprascapular area in mice. At 1 month, the highest cyclosiloxane levels were detected in the mesenteric lymph nodes, ovaries, and uterus, but all organs contained some cyclosiloxanes.

Radioactive D4 administered by inhalation at 700 ppm was widely distributed in rat tissues, but only 5-6% of the dose was retained in the tissues. Anderson, et al.[6] proposed high pulmonary and hepatic clearance, but, in another model of the data, Luu and Hutter[7] predicted accumulation in the fat depots. Mentor consulted with an independent expert, H. Crewell, who agreed with Anderson, et al.'s findings. The potential long-term accumulation of low molecular weight siloxanes, such as D4, in tissues may provide opportunities for metabolic inactivation of the siloxanes or the conversion to new toxins that accumulate with time.

Biocompatibility Testing

The biocompatibility testing below was conducted on all the major gel-filled breast implant components - the shell, the gel, and the patches. Tests were also conducted on device contact materials such as the packaging materials and foam used to texture the implant. The materials tested include the---------- shell materials in both smooth and textured implants, the ---------- included only in the textured implants, dispersion -------- , an RTV or dip coat fill used to seal the hole through which the gel is introduced into the shell, thermoforms used as packing materials, the lid for the implant container, a device contact ---------- --- -- material, a ---------- release material used to help release the shell from the mandrel, and a complete 100ml device implant tested to represent all components of the prosthesis.

1. Cytotoxicity Testing

Cytotoxicity testing was conducted using mouse fibroblast L929 cells. Most materials were tested by both the agarose overlay method in which the device is placed directly on an agar overlay of the cells, and by the USP elution Method, in which the device is extracted into Minimal medium and the extract is placed onto a lawn of cells. In both cases, the cells were observed for lysis and changes in cell morphology or cell death.

The test articles included the --------- elastomer, the dip coat fill, the -- - -------- elastomer, thermoforms (packaging material), the implant container lid, the ---------- mold release, device-contact----------, and total 100ml gel prosthesis. None of the test materials was found to be cytotoxic.

2. Short Term Irritation and Implantation Testing

The textured shell material, a thermoform, --- ---------- mandrel materials, and---------- patches were tested for irritation. Each was extracted into saline and cottonseed oil (CSO) and injected subcutaneously in rabbits. The injection sites were observed for edema and erythema. There was no significant reaction with any of these materials. A polyurethane foam device contact material evaluated by the same tests did not produce significant irritation.

The testing for some device components was adjusted to reflect their use. The mold release material (a processing aid) was sprayed onto the ---------- elastomer, dried, and extracted into saline and CSO and tested. Strips of elastomer (1mm x 10mm) with dried mold release material were implanted intracutaneously through a 16 gauge needle in rabbits. The controls were USP strips. The implants remained for 4 weeks, and the sites were examined grossly and histologically. The mold release was scored as a slight irritant based on a microscopic evaluation of capsule size and tissue reaction.

A Federal Hazardous Substance Control Act test (Draize Skin Test) was performed on the same material. For this test, the sample was placed onto abraded skin and covered with tape. The wounds were observed 24 hours later and again at 72 hours after application. The Draize scoring is for erythema and edema. No significant irritation was observed.

A 100ml textured gel implant was tested using 60cm^2 per 20ml of saline or CSO for extraction. Extracts of the complete implants showed no significant irritation (erythema or edema).

Groups of one of the ---------- patches in the CSO (cottonseed oil) group showed moderate irritation. Because the reactivity to the CSO extracts is usually higher than the reaction to the saline extracts, this may have added to the effect. FDA does not consider the result significant.

FDA concluded that none of the device components causes significant irritation.

3. Acute Systemic Toxicity Testing

Extracts for testing were prepared by using 60cm^2 per 20ml of solvent of each device component for extraction into saline and cottonseed oil. Mice were used for these experiments. The saline extracts were injected intravenously at 50 ml/kg, and the oil extracts were injected intraperitoneally at the same dose. The device components tested include the ---------- shell, a ---------- thermoform, the ---------- mold release, the ---------- ---------- a Siltex Gel-filled prosthesis, a SiTech smooth prosthesis, and ----- --- ------ patches. The animals were observed for toxic signs. No toxicity was observed.

The Ertalyte (a polyethylene terephthalate-based plastic) mandrels were extracted at the same ratios, 60cm^2 but into 5% alcohol in saline, polyethylene glycol 400, and cottonseed oil at 121°C for 1 hour. The PEG and CSO extracts were injected IP. No significant toxicity was observed in this test.

4. Hemocompatibility Testing

Hemocompatibility testing was conducted by measuring the extent of red cell lysis produced by extracts of device components. Suspensions of rabbit red cells were freshly prepared. A sample of rabbit red cells were added to each of the following tubes: a negative control tube with 10ml of saline, a positive control with 10ml of water, and 2g of test materials extracted in 10ml of saline. The tubes were incubated at 37°C for 1 hour, centrifuged, and the absorbance at 545nm was measured. The percent hemolysis is the absorbance of the sample times 100 divided by the absorbance of the positive control the positive control. The mold release material was tested after being sprayed onto 30cm^2 and 90cm^2 sections of elastomer and extracted. Both smooth and textured devices elastomers were evaluated. No significant hemolysis was seen in any of these extracts.

5. Pyrogenicity Testing

Rabbit Pyrogen Studies on a -------- Siltex Gel-Filled prosthesis were conducted by measuring rabbit temperature increases following intravenous administration of device extracts in New Zealand White Rabbits. The test article was a complete 100ml textured prosthesis extracted into 60cm^2 per 20ml of sterile non-pyrogenic saline. The rabbit temperature rise was within acceptable limits. The test materials were, therefore, considered non-pyrogenic. The -------- Smooth Gel-Filled Mammary prosthesis was tested in the same way. The device was not pyrogenic.

6. Immunotoxicology Testing

Sensitization Testing

Sensitization testing was performed on---------- ---- extured elastomer component), the dispersion coating (--------), the mold release --------- – after spraying on elastomer), and the ---------- patches (---------. The Guinea Pig Maximization test was used. The CSO and saline extracts were injected intradermally, and, a week later, petrolatum with SLS was rubbed into the site. A day later, the petrolatum was removed, and test article on filter paper was applied and removed after 48 hours. Induction was tested two weeks later using a Hill Top chamber.

Dermal reactions were observed 1, 2, 3, and 4 days. No significant sensitization was observed for any of the materials tested.

Extensive Immunotoxicity Testing

There were three groups of extensive immunotoxicity tests. In all three, testing was conducted by implanting the test materials subcutaneously in B6C3F1 mice. Three shell doses were used, $14mm^2$, $28mm^2$, and $57mm^2$. The patch was tested only at $28mm^2$. Cyclophosphamide was the positive control at 25mg/kg IP. The animals were regularly observed for any toxic signs.

In the first test, the low bleed shell was tested. The parameters evaluated were body weights, spleen and thymus weights, hematology, including RBCs, hemoglobin, hematocrit, MCV, MCH, MCHC, a differential count of leukocytes. In the spleen, IgM antibody forming cells to sheep erythrocytes, splenic T cells, $CD4^+$, $CD8^+$, and B cells were all enumerated. For total T-cell enumeration, a Thy 1.2^+ monoclonal antibody was used. All of the observations were normal except for an increase in T cells in the spleen, as determined by the Thy 1.2^+ marker and a decrease in spleen weights in the animals exposed to the low bleed shell and patch.

An additional experiment was conducted to determine the cause of the increased Thy 1.2^+ responsive cells without increases in the counted T-cells. The result was that the Thy 1.2^+ marker is non-specific and also binds to "non-immune cells." The non-immune cells type was likely to have been fibroblasts which also bind the Thy 1.2^+ antibody. Thus, there were no immunological abnormalities in the first experiment.

In the second test, the smooth envelope low bleed shell was tested after a 10-day exposure to implanted smooth low bleed shell. There were no effects on body weight, spleen or thymus weight, or thymus histopathology. The implants did not alter the response of the spleen cell proliferation response to T-cell mitogens (Con A or Phytohemagglutinin), nor was the response to allogeneic spleen cells from DBA/2 mice altered. Taken together with the first test in the series, Mentor concluded that the smooth elastomer low bleed shell did not alter the immune response.

In the third set of experiments, the textured envelope low bleed shell and valve from the Becker product (not part of this PMA) were tested. The protocols are very similar to the first set of experiments. The testing was designed to test the effects of the device implantation on immune system function. None of the implants significantly affected the immune system in these mice. There were no changes in spleen weight, thymus weight, hematology (RBCs, Hb, HCT, MCV, MCH, MCHC, or leukocyte numbers or differentials. There were no differences in the ability to produce antibodies to T-dependent sheep erythrocyte antigens. There were also no differences in the number of spleen cells, and no effects on the T-helper or T- suppressor populations. In conclusion, there were no significant effects of the test articles on the immunological response.

Platinum Toxicity

FDA believes that the catalyst used in the current Mentor breast implants is in the zero valence state and, thus, does not pose an immunotoxic risk to women.

7. Reproductive Toxicity including Teratogenicity Testing

One-generation reproductive and teratogenic toxicology testing was provided for the Mentor Silicone Gel ---------- . Teratogenic effects were followed in the F1 animals for systemic, developmental, neurobehavioral, and reproductive abnormalities. The animals were examined carefully for each of the examinations/tests conducted, and the qualitative findings and numerical results were provided. Gel was implanted at 0, 3, 10, and 30ml per kg. The control group was implanted with carboxymethyl cellulose. The F1 animals were examined for sex ratio, developmental markers, anogenital distance, pinna detachment, etc. Selected F1 weanlings were retained until adulthood, and examined for growth, motor activity, learning, and memory. There were no significant reproductive changes such as age of acquisition of puberty, sperm motility, etc. At necropsy the animals were examined for anatomical teratogenic effects. There was no significant evidence of reproductive or teratogenic effects.

8. Genotoxicity Testing

Salmonella Reverse Mutation Assay

The Genotoxicity Testing was performed using the Salmonella Reverse Mutation Assay (Ames Test), Unscheduled DNA Synthesis, the Chromosome Aberration Assay in CHO cells, and the mouse micronucleus assay. The tests were all done with and without S9 activation. The Ames (Salmonella Assay) was used to test elastomer ---------- the dispersion coat (part ---------), the mold release, low bleed shell, and extracts of the complete 100ml implant. There were no significant genotoxic effects.

Unscheduled DNA Synthesis

Unscheduled DNA synthesis was used to test the Smooth Low Bleed Gel-filled Mammary Prosthesis. The test article was a 275cc smooth low-bleed gel-filled prosthesis. The entire device was extracted into saline and into ethanol. The test article was extracted using 0.2g test article per ml of extraction medium. Neither extract stimulated unscheduled DNA synthesis.

Chromosome Aberration Assay

Chromosome Aberration Assays were conducted in CHO Cells. Saline and alcohol extracts of a low-bleed shell gel-filled prosthesis were tested. The test article was chopped into small pieces for extraction at 50°C for 72 hours with shaking. Colcemid was added 2 hours prior to harvest to inhibit cell growth. The test was performed with and without S9 activation. No increases of chromosome aberrations over the control were seen.

In-vivo Mouse Micronucleus Test

The test article is a 300cc Siltex Moderate Profile Gel-filled Mammary Prosthesis from lot 257949. The device was cut into small pieces through all layers and extracted into saline and corn oil at a ratio of 1 g of device per 5 ml of extraction solvent. The positive control was cyclophosphamide, 2.5 mg/ml. The device extracts did not increase the micronucleated cells in the marrow of injected animals. There was no evidence of genotoxicity.

9. Carcinogenicity Testing

Because of the negative mutagenicity testing and a negative mouse micronucleus test, additional carcinogenicity testing was not requested by FDA. However, Mentor provided several carcinogenicity tests which are summarized below, but the relationships of the materials to the current device materials are not clear.

Carcinogenicity in Albino Rats using ---------- Dow Corning Gels

Each of the Dow Corning silicone gels was implanted in 50 male and 50 female rats. There were also sham operated and no-treatment control groups. Solid state tumors were seen in all the implantation groups. The tumors were all mesenchymal tumors, primarily fibrosarcomas. The sham operated and untreated controls did not have tumors. All other pathology was comparable across the treated groups.

A Lifetime Implant Study with Dow Corning ---------- Gel in Rats

This experiment utilized varying levels of test material as well as the polyethylene controls. There was no increase of non-mesenchymal tumors. The authors concluded that the silicone gel does not contain a chemical carcinogen because there was no increase of non-mesenchymal tumors across the 3 dose levels tested. That is, tumors other than solid state tumors were not increased.

D. MODES AND CAUSES OF RUPTURE

To characterize the modes and causes of rupture of their device, Mentor provided the following test results and information below:

(1) independent SEM analyses
(2) re-examination of devices in Product Evaluation database
(3) updated retrieval study
(4) explant physical testing summary
(5) explant rupture failure rate analysis
(6) in-vitro biodegradation
(7) assessment of manufacturing processes
(8) assessment of surgical techniques
(9) literature review.

This memo includes a detailed summary of only the first three test reports above, which are the ones that detail the failure modes of Mentor's retrieved explanted devices. However, the key outcomes from other tests and information are briefly summarized as well.

1. Independent SEM Analysis of Failure Modes of Mentor Devices

Mentor contracted with Harry Brandon, Ph.D., Washington University, to perform an independent SEM analysis of some Mentor explanted silicone gel-filled breast implants retrieved after explantation.

Brandon was sent 39 samples from the Adjunct Study and 7 samples from the Core Study that were considered by Mentor to be representative of all the different failure characteristics that had been identified by Mentor's Product Evaluation (PE) personnel. Brandon's objective was to perform field emission SEM, with a Hitachi S-4500, either (1) to substantiate the results of Mentor's optical microscopy analysis by providing additional morphological features or (2) to visualize a failure mechanism not seen by Mentor's optical microscopy analysis.

Of the 39 devices provided by Mentor, Brandon chose 29 samples to perform SEM analysis. Of the 29 samples, 26 of these were explanted, failed devices, and 3 of these were control samples. The controls, which consisted of a simulated blade damage, a simulated scalpel damage, and a dog bone sample after fatiguing, were included for the purposes of documenting these failure modes through SEM.

The table below summarizes the findings for the 26 explanted, failed devices.

Failure Modes	**N**	**In-Vivo Years**	
		Ave	**Range**
Sharp instrument damage	8	0.5	0.0 - 1.4
Localized shell fatigue (i.e., fold flaw failure)	11	5.2	3.5 - 7.8
Miscellaneous failures *(cause unknown)*	3	6. 8	2.8 - 9.4
Long failure lines *(cause unknown)*	2	2. 6	2.0 - 3.3
Short failure lines *(cause unknown)*	2	0.1	0.0 - 0.3

The following is a discussion of failure modes identified by Brandon:

- **Sharp instrument damage failures** include both blade and needle damage. Parallel striations are evident with suspected and simulated blade damage control shells. However, the absence of parallel striations cannot eliminate the possibility of iatrogenic damage since tears initiated from needle punctures will not present parallel striations.

- **Localized shell fatigue (i.e., fold flaw) failures** result from localized flex fatigue or fold flaw mechanisms. The damage is characterized as a tapered or feathered opening, material cracking, and parallel feathering lines (i.e., characterized by a fishbone pattern in the elastomer radiating out from the failure). In some cases, there is evidence of exterior surface abrasive wear due to abutment, folding, and rubbing contact of the exterior surface. According to Brandon, when it is present, this failure mode is quite distinctive and easily identifiable in the explant samples. Inner or outer shell layer delamination sometimes occurs in the proximity of the failure area. Delamination of the inner layer is more frequent than the outer layer. The preponderance of localized shell fatigue failures occur with textured devices. According to Brandon, this is to be expected because the stress related to the folding of the shell is increased with the thickness of the shell. Textured shells are thicker than smooth shells. Thus, the stress and the ultimate fatigue related to the cycling of the fold should be exacerbated in the textured device.

- **Miscellaneous** failures are described below.
    - The **1st device** failed at 2.8 years. It was a smooth device with a long failure line. No striations were found on the failure, indicating that no sharp instrument damage was involved. However, Brandon stated that it is very difficult to examine a long failure line with SEM; so damage from sharp instruments cannot be disregarded. Also, no cracks were found on the surfaces of the device which indicates that fatigue was probably not involved in the failure. The failure line encompassed part of the shell/patch junction. Brandon proposed two possibilities for the failure: (1) the initiating incident occurred away from the shell/patch junction and propagated to that region or (2) the failure initiated at the shell/patch junction and propagated elsewhere on the shell. Brandon believed that the former was most likely because no surface cracks were found and because shell/patch junction failures usually involve fatigue in the vicinity of the failure. For smooth devices, this is an unlikely occurrence because the shell/patch junction is remote from the radius where most folding and fatigue occur. Therefore, this failure is the likely result of sharp instrument damage or local stress resulting from the implantation procedure. According to Brandon, the relatively short time to failure would tend to confirm this supposition.

    - The **2nd device** failed at 8 years. It was a textured device with a short failure line which could be examined thoroughly. No parallel striations were found, which, according to Brandon, means that the failure was not the result of sharp instrument damage. There was no surface abrasion and no surface cracking that would be characteristic of fatigue failure. A shallow surface defect was noted on the inside surface of the device in the vicinity of the failure line. This could indicate a manufacturing defect. However, it should be noted that the actual

failure line did not originate at the location of the surface depression. Brandon stated this is a longer-term failure for which no unambiguous cause could be assigned.

- The **3rd device** failed at 9.4 years. It was a textured device with a small area of the outer layer of the shell that had delaminated from the second layer. There was slight surface cracking and a pattern of fatigue lines under the delaminated section. According to Brandon, both of these, as well as layer delamination, are characteristics of fatigue failure. These facts, coupled with the longer failure time of 9.4 years, would indicate that this device failed from localized shell fatigue and, therefore, Brandon categorized it as such.

- **Long thin line failures** (for which an initiating cause could not be determined) result from specific initiation point and propagate from that point. They are problematic in terms of assigning a cause of failure because the failure initiation of the long rent may be an extremely small portion of that rent (i.e., a very short scalpel cut or a needle puncture). These can be extremely difficult to locate and identify. Brandon speculated that the initiating incident could be iatrogenic, localized stress from the surgical implantation, or a manufacturing defect. Brandon further stated that, in the case of fatigue failure resulting from local stress applied during implantation, the initiation point looks precisely identical to the propagation section of the failure line. The failure lines have the appearance of tear propagation, as seen with control samples subjected to tear test procedures.

- With regard to the **short line failures**, Brandon speculated that these devices may have failed due to localized stress introduced during the implantation procedure, a microscopic flaw from a surgical instrument, or from an unobservable defect that resulted in a weakened shell.

After performing SEM analyses, Brandon performed extraction and swelling for crosslink density at the failure site and at the adjacent unfailed region on 5 samples. Brandon found that the amount of extractable material in the damaged regions was consistently less than in the undamaged regions. This suggests that the crosslink density is higher at the failure sites, which seems to be counter-intuitive.

In summary, Brandon identified the modes and causes of rupture for 19 (73%) of the 26 explanted failed devices. For the remaining 7 (27%), Brandon identified the mode of failure (i.e., miscellaneous, long failure line, short failure line) but could not determine the cause of the failure. However, it is important to note that Brandon's analysis included samples that were specifically selected with the purpose of assisting Mentor in documenting and categorizing the different modes and causes of failure for their failed retrieved devices. Thus, one cannot draw definitive conclusions from this analysis regarding the distribution of the different failure modes or the in-vivo time frames for those failed devices.

2. Analysis of Failure Modes of Devices from Product Evaluation Database

The purpose of this study was to re-examine the devices identified from Mentor's Product Evaluation (PE) database and identify the modes and causes of failure.

The study specifically involved devices sold domestically that were returned to Mentor and designated as non-iatrogenic rupture under the categories of "Rent - Unknown Cause" (RUC) and "Not Apparent—Etiology Unknown" (NAEU). RUC and NAEU devices were those that the PE department could not determine the mode or cause of failure. There is no difference between the RUC and NAEU devices except that the NAEU category was used prior to 1994 and the RUC category was established and used since 1994. Accordingly, the combined findings for the RUC and NAEU categories were presented below (i.e., RUC + NAEU).

Of the 3048 RUC + NAEU complaints in the PE database, there were a total of ---- from domestic sales. Of these ---- complaints, ---- involved failed devices. The table below shows the overall failure mode and failure region for the failed RUC + NAEU devices.

	RUC + NAEU
	N = ----
Failure Mode	
Thin line shell failure – localized stress *(presumed cause)*	------—----
Thin line shell failure – instrument damage	-------- -
Localized shell fatigue (i.e., fold flaw)	----------
Shell/patch junction	----------
Shell/patch delamination	---------
Patch internal	--------
Combination failures	--- ------
Failure Region	
Failures involving radius region only	-----------
Failures involving (but not limited to) radius region	------- -----
Failures involving anterior and/or posterior regions only	----------

Brandon had speculated that long and short failure lines (i.e., thin line shell failures in this report) could be caused by surgical damage, localized stress, or a manufacturing defect. For the RUC + NAEU samples, Mentor was able to definitely identify those that failed due to surgical instrument damage. Mentor then discounted manufacturing defects as a possible cause of thin line shell failure because manufacturing defects did not contribute to device failure to any significant level for the Brandon study and because the only manufacturing failures found in this report were shell/patch delaminations, which were stratified out. Thus, Mentor noted localized shell damage as a possible cause of thin line failures where there was no other clearly identifiable cause of failure.

Mentor also stated that **iatrogenic** damage is more likely in the area of the radius or on the anterior regions of the device above the radius. This is because: (1) during closure of the wound,

there is a higher probability that the device will be punctured because suturing is done at the periphery of the device for inframammary and transaxillary surgical approaches. (2) Removal of the implant is typically at the periphery of the device based on the fact that inframammary and transaxillary placements are more frequent than periareolar approach. (3) Device placement procedures involve pushing the device through the incision using 1-2 fingers to force the device into the surgical pocket. This results in localized stress in the radius area.

Mentor also stated that there is also a propensity for **non-iatrogenic** failures in or close to the radius. Although some may not be in the radius region, non-iatrogenic failure related to folding/wrinkling of the shell result in localized fatigue failure, which is most prevalent in the radius region. However, there were other failure modes, such as shell/patch failure, which involve a specific failure area away from the radius.

For each failure mode below, FDA provided a general description followed by the specific findings from Mentor's re-analysis of the RUC + NAEU devices.

Shell Thin Line Failures – This failure mode involves only the shell. The failure is caused by (1) cutting or puncturing with a sharp instrument during implantation or explantation of an implant or (2) tears resulting from localized stress that extends the shell beyond its elastic limits (ultimate elongation). Although not stated by Mentor in this analysis, another causes could be in-situ procedures (e.g., biopsies). A defining characteristic of all thin line failures is that each side of the failure is a mirror image of the other.

If a surgical instrument cut/puncture is created but not detected during implantation, it will propagate as a tear over time. The shell tearing results from stresses applied to the device during implantation (i.e., forcing the device into the pocket) in the presence of a cut/puncture.

On the other hand, localized stress could be induced by the surgeon during implantation and could cause tears even without a puncture/cut. During implantation, the surgeon forces the implant through the incision into the surgical pocket with 1-2 fingers, causing localized stress, particularly on the radius region. In addition, after inserting some of the device into the pocket, the surgeon squeezes the device to expand it into the pocket, likely to a point close to the ultimate elongation limit for the material. This could permanently deform/weaken the shell in the radius region, resulting in a thin line tear.

Whether due to a surgical instrument cut/puncture or localized stresses, Mentor surmises that the amount of propagation is related to the stresses placed on the device based on the patient's lifestyle. Over time, the failure can grow and encompass more of the anterior region or even proceed to the posterior region.

Of the ---- explanted devices re-examined, ---------- had thin line shell failures – --- due to instrument damage and ---- due to localized stress. All --- devices that failed intraoperatively were those categorized as thin line shell failures. In-vivo times were available for - of --- thin line shell failures (instrument damage). The data showed that - failed at 0-5 years and - failed >10 years. In-vivo times were available for --- of ---- thin line shell fail- res (localized stress). The data showed that --- failed at 0-5 years, --- failed at 6-10 years, and - failed at >10 years.

Of the ---- total thin line shell failures, --- were Siltex and --- were smooth devices; however, the impact on failure by shell surface can not be assessed based on number of devices with an unknown time to failure. 71% of the failures involved (but were not limited to) the radius region. Over time, the failures were observed in more regions of the device, which is consistent with expected propagation of failure lines over the shell surface.

Localized Shell Fatigue Failures (Fold Flaw) – Mentor stated that there is strong evidence that supports that this failure mechanism results from shell folding. If the shell folds in the anterior surface and that fold extends close to or into the radius, a high stress area will be formed at the end of the fold close to the periphery of the device. Flexing the device at the radius will cause the high stress area at the end of the fold to "roll" as the stress is applied and removed. Over time, the cyclic stress causes the shell material to fatigue and fail. Small holes form in the failure area, leading to a larger opening. Many of the failures have fishbone patterns, ragged and disorganized. In a few cases, delamination of the inner layer of the shell is evident around the failure, and a few showed delamination of the outer layer; these delaminations are in a small area (i.e., mm in size).

Shell abrasion was seen in many of the fold failures. The abrasion marks were typically in a "V" pattern with failure at the bottom of the "V." The folds generally extended from the apex region of the anterior surface and end at or near the periphery of the device in or near the radius area on the external surface of the device. Mentor stated that shell abrasion was not a cause of the failure, but an artifact of the failure mode because there are no failures directly within the abrasion lines that extend away from the failure area.

Mentor believes that there are two independent causes of wrinkling/folding. First is inadequate gel volume that could cause formation of fold or wrinkle in the shell. Second is inadequate size and shape of the surgical pocket.

Of the ---- explanted devices re-examined, ---------- had localized shell fatigue failures. The in-vivo times to failure were --- devices at 0-5 years and --- devices at 6-10 years. There were no failures through 1 year, which is expected because fatigue failure takes time to develop. All failures involved (but were not limited to) the radius region. Of the --- localized shell fatigue failures, --- were Siltex and - were smooth devices. Mentor attributed the predominate number of Siltex failures to the Siltex thicker shells possibly being more susceptible to folding.

Shell/Patch Junction Failures – This is failure of the shell/patch junction. The patch is attached to the outside of the posterior shell and overlaps the shell hole for the full circumference. The overlap area is, thus, thicker. At the outer periphery of the patch, the thickness reduces to that of the shell. When stress is applied to this area, the shell will elongate to a much greater extent that that of the shell/patch combination. The likelihood of failure is increased by cyclic stress.

Of the ---- explanted devices re-examined, ------- --- had shell/patch junction failures. The in-vivo times to failure were --- devices at 0-5 years and - devices at 6-10 years. This failure was not observed during the intraoperative period, which is expected because it takes time to develop cyclic stress-induced failures. Of the --- shell/patch junction failures, --- were Siltex devices and - was a smooth device. Mentor expected this because the textured patch is large and extends

closer to the periphery of the device and the smaller patch on smooth devices. Thus, the patch/shell junction is closer to the area of higher flexural stress.

Shell/Patch Delamination Failures – This failure mode involves failure of the bond between the shell and patch. The strength of the bond is directly related to the vulcanization process, which occurs during manufacture.

Of the -----explanted devices re-examined, ---------- had shell/patch delamination failures. The in-vivo times to failure were - devices at 0-5 years and - devices at 6-10 years. Of the --- shell/patch delamination failures, all were Siltex devices. Mentor attributed this to the fact that the larger patch on Siltex devices are more difficult to bond.

Patch Internal Failures – This is a thin line failure of the inner patch/shell junction in the textured area of a patch. This area could be susceptible to the same failure/propagation mechanism as other parts of the shell. Although an infrequent occurrence, the failure is likely due to the fact that the patch bond area does not allow for this internal region to bend or wrinkle as much as the unconstrained areas of the shell.

Of the ---- explanted devices re-examined, -------- had patch internal thin line failures. -- of these failures occurred at 0-5 years and - at 6-10 years.

In summary, for the------RUC + NAEU devices examined, Mentor determined the modes and causes of rupture for ----------of the ---- failed devices. For an additional ---- devices -------, Mentor presumed that the thin shell failures were due to localized shell stress. As explained above, Mentor determined that manufacturing defects were not the probable cause of failure. This leaves only local shell fatigue as the remaining, most likely, mode of failure. The remaining --------- involved a combination of defects for which Mentor analyzed the cause of each individual defect in each implant. However, Mentor was not able to identify the initial and primary cause of failure, so no conclusions could be drawn concerning the specific modes and causes of failures in these implants.

ADDITIONAL ANALYSES

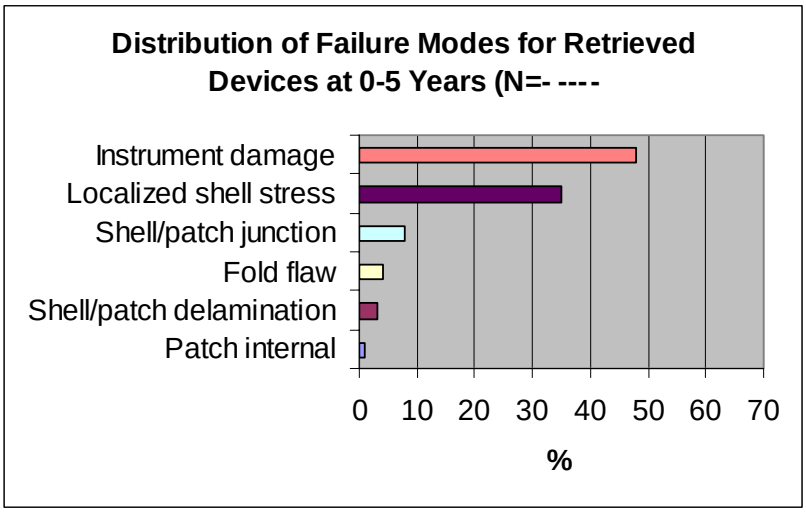
The analysis above did not include retrieved failed devices with obvious damage due to surgical instrumentation (i.e., Mentor's RUC and NAEU were failed devices with an unknown cause of failure when originally entered into the PE database). Mentor provided an additional analysis combining the RUC + NAEU data with data from devices previously determined to be iatrogenic failures (i.e., sharp instrument damage) from the *Iatrogenic (User Related)* category in their PE database. This was the only other category in Mentor's PE database observed by their laboratory as having device failures. By combining the previously determined iatrogenic failures from the *Iatrogenic (User Related)* category with the RUC + NAEU iatrogenic failures, Mentor believed that they could provide a more complete summary of failure modes from domestic, failed devices from their PE database. Accordingly, Mentor added all ---- domestic, failed devices from the *Iatrogenic (User Related)* category into the "thin line shell failure – instrument damage" failure mode category.

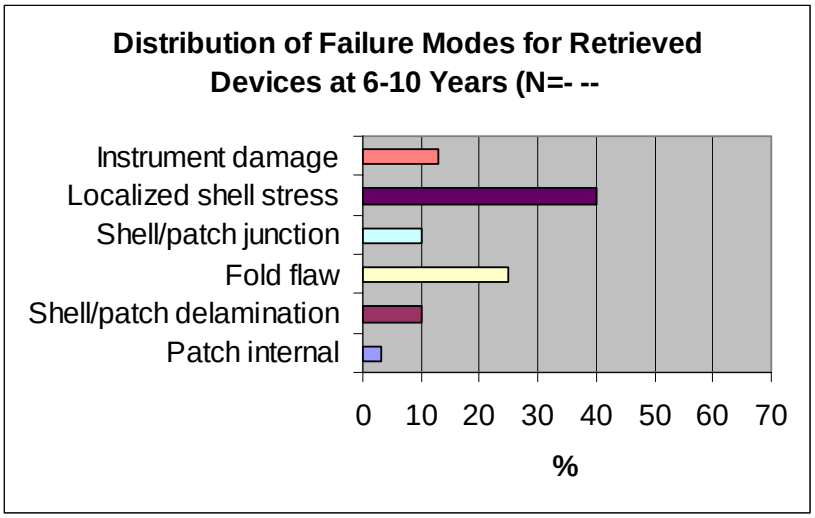
The table below summarizes the number and percentage of retrieved devices that were observed with the specified failure mode. There were --- devices that had combination failures, which are not included in the table or bar graphs below. As described in the paragraph above, devices with sharp instrument damage also include those from the *Iatrogenic (User Related)* category. All other failure mode data reflect only RUC + NAEU data. These data cannot determine the time at which a given failure mode will occur because the data are based on only a small collection of retrieved implants that were available for analysis. The data can, however, be used to present the distribution of device failure types observed in this sample at particular time frames.

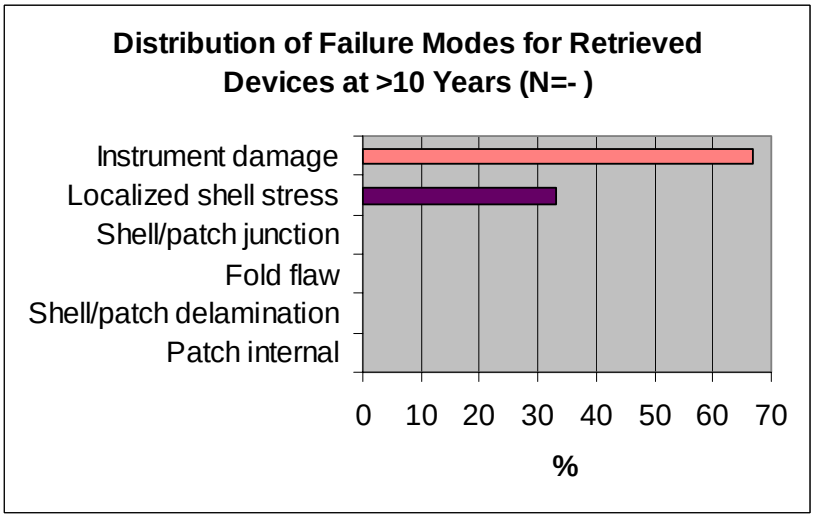
Failure Mode	**# (%) of Retrieved Devices Ruptured During Specified In-vivo Time**		
	0-5 years	**6-10 years**	**>10 years**
Thin line shell failure - instrument damage[1]	------- -----	-------- -	-------- -
Thin line shell failure - localized shell stress from implantation procedure *(presumed cause)*	----------	----------	-------- -
Localized shell fatigue (i.e., fold flaw)	---------	----------	--------
Shell/patch junction	---------	---------	--------
Shell/patch delamination	--------	---------	--------
Patch internal	--------	--------	--------
Total	------- ----- -	------- - -- -	----------

[1]RUC + NAEU data combined with *Iatrogenic (User Related)* data.

The following bar graphs reflect the percentage (or distribution) of the failures modes for the different time intervals shown in the table above.







3. Mentor Retrieval Study Report Addendum

In their original PMA submission, Mentor provided an analysis of retrieved explanted devices from the Core Study. In their August 2004 amendment, Mentor provided a re-analysis of these data in response to the 4/14/04 major deficiency letter. The purpose of Mentor's retrieval study was to evaluate explanted devices from their Core Study and to document failure modes.

As of 7/9/04, a total of 1,995 devices were implanted in the Core Study, which was comprised of 1260 Smooth Round Moderate Profile Gel and 735 Siltex Round Moderate Profile Gel). 57 devices (42 smooth and 15 textured) explanted through 3 years were included in this study. Of the 57 devices, 46 (81%) had no abnormalities. Below is a summary of the failure modes and corresponding time(s) to failure for the remaining 11 devices.

Failure Modes	# (%)	In-Vivo Time
Sharp instrument damage	-	3 @ 0 days; 2 @ 97 days; 1 @ 351 days; 1 @ 406 days
Unknown cause of rent	-	NA
Crease fold (no opening)	-	965 days

As noted in the table above, there are 10 devices identified with ruptures and, conceivably, these should have been identified as such in the Core Study dataset. Mentor stated that 2 of these ruptured devices were included in the Core Study dataset as confirmed bilateral ruptures in 1 patient. The other 8 devices were not included in the Core Study rupture rates based on the following explanation from Mentor: 4 devices wer damaged intraoperatively and immediately replaced during the surgery; 2 devices (---------- ----------) were noted as being removed for capsular contracture; and 2 devices (---------- --------- as being removed due to patient request/size change. (It is the explanting surgeon's visual assessment at the time of explantation which has determined the final rupture status – either intact or ruptured – for the purposes of the Core Study.)

Mentor conducted material property testing on the failed devices. All samples passed ASTM D412 and F703 specifications.

Mentor presented summary data on the explanted devices, including indication, surgical approach, device placement, pocket irrigation, and incision size, stratified by smooth and Siltex devices. Mentor also provided the reasons for removal identified by the physician, stratified by smooth and Siltex devices. However, Mentor stated that they did not perform any analyses to determine whether or not any of the variables had an impact on rupture because of the small sample size, which would not allow for a meaningful analysis.

Mentor drew no conclusions on the data above. Instead, Mentor stated that they will continue to analyze explanted devices as they are returned to them throughout the duration of the Core Study.

4. Other Testing and Information

Mentor evaluated the changes in shell physical properties over time for in-vivo samples taken from 2 sources: (1) a sample of 57 explanted devices from their Product Evaluation (PE) database (which contains mostly devices from the Adjunct Study) and (2) all 57 explanted devices (ruptured and intact) from the Core Study. Ruptured devices were primarily chosen from the PE database because they represented devices that were expected to have been stressed the most. Iatrogenic ruptures were not selected because they usually are not in the body long enough for the shell physical properties to change. The physical properties (i.e., ultimate tensile strength, break force, % elongation, patch/shell joint strength, and tension set) were evaluated separately for each of the textured and smooth devices for each of the PE and Core Study samples.

The PE explant testing results indicated that, in general, the shell physical properties remain either fairly constant during their time implanted, or experience a slight reduction in their physical properties during an initial implantation period, but then usually level off and remain fairly constant out to 9.5 years in-vivo. On the other hand, the Core Study explant testing results indicated that, in general, the device shell properties for smooth are unchanged over the 3 years of available in-vivo time. However, Core Study Siltex devices show a decrease in property over the early time period but then become fairly constant for much of the rest of the available in-vivo time. As a note, the findings for the PE samples appear to be consistent with what Brandon has discussed in numerous published articles that the physical properties decrease slightly and then reach equilibrium, presumably within the first few years after implantation. Mentor stated that it

is not clear what conclusions can be drawn from this other than there are property changes over time, but currently available data in other reports indicate that property changes do not appear to be the cause of device failure.

Mentor evaluated the effect of a simulated physiological environment on shell properties. Whole Siltex Round Moderate Profile implants (100cc) were immersed in saline (control solution) or--------- serum (the test solution), and incubated at 37°C for ≈60 days using a mass-to-volume ratio m/v = 1:2.5. ------- --------- was chosen to simulate the composition, including lipid content, of the extracellular fluid within the fibrous capsule that is in direct contact with the implant in the patient. Time or duration of exposure was chosen to reproduce the longest experimental time encountered for a single cyclic fatigue device test. The endurance limit test is the longest cyclic fatigue test and requires 23 days of continuous exposure to the in-vitro environment (10^7 cycles x 5 cycles/sec = 23 days). This test time was doubled for the exposure experiment (56 days) to develop a response to the worst possible case. The time is not representative of long-term in-vivo implantation. M/V ratio of 1:2.5 was not chosen to reproduce the in-vivo environment; it was selected arbitrarily to approximate the ratio used for cyclic fatigue testing, typically between ≈1:5 and ≈1:10 volume ratio. Mentor did not consider the M/V ratio to be a critical experimental parameter for various reasons. At days 0, 1, 3, 7, 14, 21, 28, 35, 49, and 56, multiple devices were sampled and weighed. The shell components were subjected to: tensile testing; elongation; stress at 100%, 200%, and 300% elongation; break energy; and Young's modulus. The gel components were subjected to rheology testing.

The results showed no statistical difference in weight change (associated with potential gel bleed and lipid infiltration), shell material properties, or gel rheology properties for samples incubated in either saline or ---------- Mentor concluded that the use of saline and ---------- for cyclic fatigue testing would yield the same result and, thus, saline is acceptable for in-vitro conditions representing the in-vivo environment.

Mentor evaluated whether the manufacturing release specifications related to particle defects and bubbles were related to device rupture. Mentor reviewed the product complaint database for silicone device ruptures and found that no assignable cause of any rupture, rent, or cut in a device could be attributed to the presence of an embedded particle or bubble. However, Mentor performed two specific studies to address this issue. First, Mentor evaluated the effect of particle defects, of specific size, on the physical properties of HTV gel shells. The samples were cut from shell assemblies identified by inspectors as having different ranges of particle sizes in the shell. The conclusions were that particles ⩽-------- in diameter in the shell layers meet shell property specifications. Second, Mentor evaluated the effect of bubbles on the physical properties of HTV gel shells. Currently, Mentor's manufacturing specification states to reject shells with bubbles --------- in diameter. In this report, Mentor evaluated the impact of bubbles ---------- in diameter. Mentor found that bubbles in that range do not adversely affect shell physical properties. Mentor stated that these studies indicate that particle defects and bubbles do not contribute to device rupture.

Mentor performed preliminary testing to simulate fold flaw and to determine the conditions under which it develops as a failure mode. The testing involves 8 - 325cc Siltex Round Moderate Profile Gel breast implants. Each device was placed in the test chamber and immersed in saline. The test fixture probe (foot) was positioned at the center of the device to introduce a fold parallel to the diameter of the device, resulting in a crease formation on the radius. The probe was fixed within the crease and does not move through the crease. The crease formed on the device radius was compared to a small "pinch" or "wrinkle" of the shell with ≈1-2 mm width. The cyclic crease fold test incorporates a bimodal stress event. The probe provides a constant static compression load. The other stress provides cyclic transverse strain of the crease using a motor driven actuator. Accordingly, the "rolling wrinkle" is designed to induce cyclic failure at the radius. To date, all 8 samples have reached 12M cycles without visible signs of fatigue stress. Mentor considers this to be equivalent to 2 years of in-vivo loading (5 hours of walking/day at 1 step/sec = 1 year). Mentor stated that the lack of failure is supported by their belief that a pure cyclic fatigue failure takes time to develop. Mentor will continue the testing until the samples have failed, at which point the cycles to failure will be analyzed and used for a comparison to their PE data.

To assess the surgical techniques related to rupture, Mentor subjected both control devices and devices to simulated iatrogenic procedures, as well as to mammography-induced compression. The simulated surgical insertion procedure was performed by a trained plastic surgeon and involved insertion of the device through a 2.5cm incision in nylon reinforced silicone elastomer. Minor scalpel damage was simulated on the radius of the shell with a surface scratch (≈1" and ≈0.0005" depth). Major scalpel damage was simulated on the radius with a puncture (≈0.025" length). Suture needle puncture was simulated by a puncture through the radius of the shell. Mammography was simulated by a trained radiology technician using a mammograph and repeatedly performed to accumulate 40 events.

Following simulated usage, uniaxial (parallel plate) fatigue testing was then performed on the samples at 40 lbs at 1 and 5 Hz, with a 10-lb holding load, in physiologic saline solution at 37°C. Based on the limited available testing performed (i.e., small sample size and a single load level), Mentor stated that (1) the results showed that the simulated surgical insertion procedure and mammography diagnostic procedure did not affect the fatigue life as compared to the control devices results. (2) Minor scalpel damage (≈1" and ≈0.0005" depth) had no apparent effect on fatigue life, but major scalpel damage (≈0.025" length with full penetration) resulted in a lost of ≈99% of fatigue life. (3) Surgical needle puncture damage through the shell resulted in almost immediate failure of the implant, with a >99% loss of fatigue life.

To further assess surgical techniques related to rupture, Mentor evaluated the data available in the Adjunct Study database. The database showed ---- device ruptures since 1985. Mentor performed a statistical analysis on the ---- devices that had postoperative ruptures and evaluated the relationship between rupture rate and parameters associated with surgical implantation. The populations included were the total combined population, revision augmentation subpopulation, and the reconstruction subpopulation. Mentor's findings are summarized below.

- Surgical approach has no influence on rupture rate for all populations and subpopulations.

- Device placement has a statistically significant influence on rupture rates, with submuscular placement being associated with a ------ higher rupture rate than subglandular placement for many of the studied populations. However, it does not appear to influence the rupture rate for smooth devices (any indication) or reconstruction devices.

- The results indicate that there is a higher failure rate for larger devices, but the trend is not strong. Mentor stated that this may indicate that the limitation of incision size imposed for cosmetic sake is not large enough to accommodate larger size devices. Another contributing factor is likely to be that larger devices may have a greater tendency to fold or wrinkle. Folding and wrinkling can contribute to cyclic fatigue failure in those areas.

- Incision size has no influence on rupture rate for all populations and subpopulations. One would expect that, for a given size of incision, as the volume of an implant increases, more stress would be required in the implantation procedure, more damage would be done to the implant shell and, consequently, a higher frequency of failures would result. To address this finding, Mentor stated that they still believe incision size is a critical factor but that surgeons are apparently making the "logical" adjustment (i.e., with larger implants they are making larger incisions). Thus, no correlation between incision size and frequency of failure across all populations and subpopulations was found in this analysis.

- Smooth devices tend to have ---------- higher rupture rates than textured devices. The reconstruction subpopulation showed a non-significant finding but this was because the number of smooth and textured devices, when reviewed separately, was too small to statistically analyze.

In terms of their **literature** review, Mentor cited references that attributed failure to: implant handling before the surgical procedure; the implantation procedure (e.g., stress and deformation during insertion, local weakening of the shell where the surgeon's fingers force the implant through the breast incision); in vivo processes (e.g., fold flaw); trauma to the breast (e.g., breast massage, closed capsulotomy, patient injuries in the chest area, surgical revisions, multiple mammograms); other surgically induced damage (e.g., breast biopsies, needle localization procedures, cyst aspirations); increasing length of implantation; implant type; manufacturing defects; and the explantation procedure.[8,9]

The literature showed that a major factor impacting shell integrity was surgical damage, which is consistent with Mentor's testing. The literature discusses localized weakening of the implant caused by the surgeon's fingers placing pressure on a specific area of the device during implantation.[10,11]

The literature is conflicting with regard to whether or not mechanical strength of the shell decreases over time. Studies from some investigators[12,13,14] suggest that implant duration correlates with increased failure rates. These investigators hypothesized that the degradation in mechanical strength over time is the result of progressive cyclic mechanical stress, which creates and exacerbates tears at the sites of thin areas, folds, and/or defects where stress is concentrated in silicone elastomer shells that have been weakened by the infiltration of silicone fluid over time in-vivo. However, other investigators[11,15,16,17,18,19] have demonstrated that implant failure does not result from in-vivo degradation of shell

mechanical properties and that these properties were essentially independent of implantation time. Based on these studies, Brandon and colleagues have concluded that "degradation of shell mechanical and chemical properties is not a primary mechanism for implant failure."[18] Mentor's testing showed that the physical properties do not change over the reported in-vivo times.

In addition, literature studies also show that diffusion of non-crosslinked silicones from implant filler into shell impacts strength.[20,21] However, some investigators believe that there is an initial decrease in properties due to the diffusion of non-crosslinked silicone from the gel into the shell, followed by equilibrium with the first few years and that there is no change in shell chemistry or that this swelling is a risk factor for rupture.[10,15,,22,23]

5. Mentor's Proposed Next Steps Based on Findings

This section summarizes Mentor's proposed changes to the device design, manufacturing, or labeling, as well as any additional analyses that they intend to perform based on the modes and causes of rupture findings.

- Mentor stated that the failure modes most directly related to surgical procedures are instrument damage, localized shell stress, and fold flaw (related to size and shape of surgical pocket). The labeling currently includes some information/warnings to avoid damage during surgery and to avoid making too small of an incision. Mentor stated that they believe it is critically important that the surgical pocket created during the implantation procedure be the proper size and shape. Thus, Mentor will include warnings about the importance of the pocket size and shape and the consequences of not providing one. Currently, the physician labeling includes the following surgical and implant sizing information: "A well-defined, dry pocket of adequate size and symmetry must be created to allow the implant to be placed flat on a smooth surface."

- Mentor will add a segment to their proposed training program regarding insertion techniques and the various failure modes resulting from some of these surgical practices. The training segment will include photographs of failed devices, as well as copies of micrographs that depict the different failure modes. The training will also include information regarding proper surgical pocket size and shape.

- Mentor proposed to begin an in-vitro study, involving physicians, to determine the optimum size of incision for the various sizes of implants. The resulting recommended sizes of incisions for each device size, or range of sizes will be presented in the training segment and will be included in the labeling.

- Mentor has an ongoing project to develop and evaluate an "introducer." This instrument will be used to insert the device through the incision, with the goal to eliminate the extreme localized stress put on the device by the surgeon's fingers as it is pushed into the surgical pocket. The introducer has not yet been designed and is not included in this PMA application.

- Because shell fatigue failures (i.e., fold flaw) have been observed primarily with only textured devices, it could be assumed that residual stresses in the texture layer could contribute to the failures. Mentor is currently conducting a long-term, in-vitro study to assess whether or not an alternate texturing process could reduce this failure mode. Mentor also has on-going crease testing to evaluate fold flaw.

- Mentor believes that one possible way to mitigate patch/shell failures is to reduce the patch size so that the stress change occurs over a wider area (i.e., the patch/shell junction is moved further away from the radius area of the device). Smooth devices have a small patch remote from the radius area. Mentor is conducting a project to optimize the patch size and for each respective shell to minimize the stress at the patch/shell junctions. Additionally, they are evaluating the use of a "contoured patch" which provides a smooth transition between the patch and shell.

- Mentor believes that one possible way to mitigate patch internal failures is to modify the texturing process. If a process for texturing could be devised to permit a smaller patch, these failures might be reduced. Mentor is currently conducting a study to assess the feasibility of providing a new texturing process. This will be a long-term development process and is not part of this PMA application.

- Shell/patch delamination failure is considered rare. Shell/patch strength and permanence is related to the vulcanization process for producing the bond. Mentor plans only to monitor for this failure because of how infrequent it occurs.

6. Summary

Through their explanted device retrieval studies, Mentor provided information regarding the modes and causes of rupture for devices implanted for a range of in-vivo times.

Failure modes associated with surgical technique include: (1) sharp instrument damage that causes immediate or subsequent rupture; (2) localized stress that causes weakening in shell; and (3) creation of fold during implantation that leads to abrasion and subsequent rupture.

The retrieval study data above show that the observed failures at the earlier timepoints were due to surgical instrument damage. Mentor stated that the longer-term failures attributed to surgical damage could have been due to a delayed intraoperative damage, explantation instruments, or instruments used during in-situ procedures (e.g., cyst biopsy). Mentor also clarified that, although a retrieval study analysis may be able to determine whether an implant was damaged by a surgical instrument, one cannot determine, with certainty, when it occurred. Therefore, it is possible that the failures due to surgical damage that were observed in devices implanted for longer time periods may have occurred at the time of implantation and were just not detected, or they may have occurred later, as a result of an invasive procedure that was performed after implantation surgery.

With respect to the localized shell stress failures, Mentor categorized these through an elimination process. Brandon stated in his SEM study that this type of failure can occur from sharp instrument damage, manufacturing defect or local shell stress. Mentor eliminated

manufacturing defect as a potential source of these failures based upon examination of the failed devices and the fact that there are only one or two failures per lot. Manufacturing problems would result in more failures per lot as explained earlier in this document. No evidence of sharp instrument damage could be found on the failed devices. This leaves only local stress as the probable source of these failures. Although Mentor provides a reasonable argument, they did not provide definitive preclinical data to support their argument.

With regard to shell/patch junction and shell/patch delamination failures, Mentor is exploring design and manufacturing changes. However, Mentor will only monitor patch internal failures due to their low numbers. Mentor believes that these manufacturing-based failures are not related to current quality control measures.

With respect to fold flaw failures, the mechanism by which it occurs is described to be a crease or wrinkle in the shell that, under in-vivo cyclic loading, eventually leads to a shell opening. However, the data show scattered timepoints for development of the fold flaw failures. While literature reports that the surgical implantation procedure may induce a fold in the implant, it is not known for certain whether the reported fold flaw failures were originally caused by the surgical implantation procedure or some other unknown factors that lead to the development of the fold.

The issue of when pure cyclic fatigue occurs remains unanswered. The current data do not show devices rupturing from pure cyclic fatigue. Therefore, it remains unknown whether or not there is physical or chemical property degradation that may lead to the cyclic fatigue and eventual rupture of the devices. Mentor provided the following detailed discussion regarding this issue.

> Fatigue failure in silicone elastomers is generally due to the growth, under cyclic loading, of a minute crack or defect in the material. In the early stage of the failure process, a single defect that will control the fatigue life is first created in the material. At this stage, this incipient rupture is very small (in the micron range), is often not visible in the material, and does not alter the measured macro mechanical properties of a test specimen or device made from the material. As cyclic loading continues, the incipient rupture grows and enlarges due to the continuing physical degradation that occurs at its ends. However, for many cycles of loading, the amount of extension of the incipient rupture is extremely small, and it continues to have negligible effect on the mechanical properties. Even at this stage, it remains very difficult to detect by visual inspection.
>
> On the other hand, the process of extension of the rupture is non-linear and its growth eventually starts to accelerate. Within a relatively small number of cycles of loading prior to actual failure, the rupture becomes large enough to change the mechanical properties of the material, for example, reducing the effective elastic stiffness (stress-strain response) and the strength. In addition, the rupture may now become visible during inspection. It is only during this latter stage that physical degradation becomes apparent in measurements of the mechanical properties of the material. Within a relatively small number of cycles of loading prior to actual failure, the rupture will then extend to a critical length, and the material will fail. Thus, a feature of fatigue failure is that little effect of load cycling is seen on the mechanical properties for many cycles of the process. Then, towards the end of the material's life, an effect becomes apparent and the material's stiffness and strength become

degraded. The magnitude of this effect accelerates as the process continues, and the reduction of stiffness and strength becomes more and more dominant until failure occurs.

The question that remains is whether physical property degradation contributes in a significant way to the failure process described above or whether it is secondary effect of the process. The answer to that is not known for certain; there are only theories. Mentor stated that device compliance increases with the number of cycles shown by the decreasing distance between the plates to maintain a given applied load. This increase in compliance can be attributed to a reduction in the elastic stiffness (same stress produces greater strain) of the device material. However, there is a large change in the device compliance at the beginning of the test in the first 200,000 cycles. After that, the change in compliance per cycle is much less. This behavior is opposite to what is observed for the degradation of properties due to fatigue damage, where the rate of reduction in elastic stiffness of the material would be expected to gradually increase during the test, not decrease. It is not certain that this observed effect during the initial phase of cyclic load testing of the device is divorced from fatigue damage. However, one explanation is that the reduction of elastic stiffness during cyclic loading of the device up to 200,000 cycles is caused by the failure of vulnerable cross-links in the elastomer. When this happens, one sees significant effects on the elastic stiffness of the material at the beginning of the cyclic loading test because the most vulnerable cross-links break first in significant numbers. However, as cycling of the load continues, fewer and fewer of the remaining cross-links break until very small numbers of them are failing and the elastic stiffness of the material changes more and more slowly. This picture is consistent with the observed change in compliance of the device during load cycling.

Therefore, Mentor concluded that a degradation of the elastic stiffness (stress versus strain response) of the material does occur during the cyclic loading but that the associated rate of change of the elastic stiffness decreases as the number of load cycles increases. This degradation of elastic properties is notable but does not seem to be connected with the ultimate cyclic failure of the device during load cycling. The reasoning for this conclusion is that all known fatigue damage processes accelerate as the number of load cycles increases and final failure comes at the stage where the mechanical properties are degrading most rapidly. Because the tensile properties at the radius are decreasing slowly and steadily and that degradation is not accelerating, it is concluded that the steady decrease in the physical properties can only be a secondary effect in the failure mechanism. This property degradation may play some role in the final stages of testing just before the device fails, but it will play a minor role in the fatigue life of a device.

In terms of characterizing ruptures due to pure cyclic fatigue, should they appear in the retrieval studies, Mentor stated that those failures can often be identified by the time to failure (longer than a few years), the presence of whitish opacity of fatigued areas in the immediate vicinity of a shell fold, and/or the presence of small microscopic surface cracks in the region close to the failed area. Based upon the fatigue failure mechanism process described above, significant physical property reduction may not be seen even in failed devices in areas away from the failure. The only time when one might be expected to see a noticeable change in shell physical properties of a failed device is if an area containing small cracks is sampled. As for chemical degradation, there is no reason to believe that saline

immersion during fatigue testing would lead to any relevant chemical changes, but Mentor continues to include chemical testing as part of their retrieval studies.

As an additional note, until retrieved devices are observed to be ruptured due to pure cyclic fatigue, the appropriateness of a fatigue test methodology cannot be assessed.

Mentor also provided their prediction on what may occur with regards to long-term modes and causes of rupture, as a whole, based on their current data. Mentor acknowledged that their implants will have a finite in-vivo life. Mentor believes that the data indicate that the implanted devices will fail in a bimodal distribution. Initial failures will occur in the first --- years, with most occurring before --- to --- years. These include thin line failures of the shell, localized shell fatigue, shell/patch junction failures, and shell/patch delaminations. When the second mode of the bimodal distribution begins, Mentor stated that it will likely be marked by failures of ever-increasing numbers of devices. The failure data show that this has not yet started to occur. Because the second phase of device failures has not begun, or, if it has, the number of failing devices is so small that it cannot be detected, then no statement regarding the mode or cause of the failures in the second part of the bimodal distribution can be made.

Mentor believes that the remaining causes of failure for the devices that survive beyond 15 years will be (1) cyclic fatigue of the shell or shell/patch junction and (2) sharp instrument damage related to biopsies, breast exploration, or explantation of the devices for reasons other than the failure of the device itself, with the bulk of them failing due to cyclic fatigue. Because of the lack of longer-term retrieval data, Mentor was not able to provide data to support their hypotheses that failures will occur in a bimodal distribution or that long-term failures will be due primarily to cyclic fatigue.

E. FATIGUE DATA

Below is a summary of the fatigue testing and analysis provided by Mentor.

In addition to the testing described below, Mentor also provided an additional fatigue testing report which evaluated a hemispherical device cage/platform that allowed for stressing of the anterior region of the device. Although this testing was not completed on the worst case device (i.e., smallest size with thinnest shell), the observed failures occurred in the radius, which Mentor believes confirms the applicability of the parallel plate test results. This report is not summarized in this review memo.

1. Cyclic Fatigue Testing of Mentor Implants

Smooth Round Moderate Profile (100cc), Siltex Round Moderate Profile (100cc), and Siltex Round High Profile (125cc) were chosen for fatigue testing as representative of Mentor's product line. All implants tested were final, sterilized versions with the minimum allowable radial shell thickness (-------- for smooth implants and -------- for textured implants).

The **monotonic (static) testing** was performed using Instron equipment with a parallel plate fixture ("uniaxial") in an air environment at 23°C. Mentor chose an air environment at 23°C to be consistent with the test set-up for their material property testing. Foam sheeting was placed between the device and plates to prevent abrasion. All static testing was conducted in load control in a range of 0-500 lbs and at a rate of 0.25 lbs/sec.

The **fatigue testing** was performed using Instron equipment with an uniaxial test fixture in a test chamber containing circulating physiologic saline solution at 37°C. This set-up focuses the stress on the radius of the device. The implants were placed between parallel plates. The top plate applies an axial compressive load to the implant. Foam sheeting was placed between the device and the plates to prevent abrasion. Fatigue testing of samples was performed at 1 Hz for all higher loads and at 5 Hz for the lower loads. The applied loads ranged from 20-100 lbs. A minimum of 3 implants for each style was tested for most load levels. Mentor justified testing at 5 Hz by comparing fatigue results conducted at 1 Hz and 5 Hz for 40 and 80 lbs. Runout (RO) was defined as 10M cycles, which is consistent with commonly accepted practice in cyclic fatigue testing.[24]

The acceptance criterion was based on the maximum load expected during walking or jogging, which is assumed to be the worst case fatigue activity. The resultant in-vivo load amplitude or force during walking/jogging was estimated from consideration of a free body diagram not at rest where an upward motion of approximately 1 ft experiences deceleration due to gravity. The resultant force is equivalent to twice the gravitational mass of the device. Mentor used 1.04 g/cc as the density of silicone for conversion of device volume to mass. For the 100cc devices tested, the expected in-vivo load is 2(100cc)(1.04g/cc)=208g or 0.46 lbs. For the 125cc devices tested, the expected in-vivo load is 2(125cc)(1.04g/cc)=260g or 0.57 lbs.

The results were:

	Smooth Round Moderate Profile (100cc)	Siltex Round Moderate Profile (100cc)	Siltex Round High Profile (125cc)
Ultimate Static Load[1]	------ --- ----	------ --- ----	----------
Endurance Load Limit at 10M cycles RO	---------- ---------- ----- -------- - -- -------- -----	----------	--------
Expected In-vivo Load	------ - -	------ - -	------ - -
Safety Factor for fatigue testing	-----	-----	-----

[1]Static failure loads are greater than that expected during mammography (55 lbs). As further rationale for the results, Mentor stated that a worst case comparison of a women weighing 300 lbs would have approximately 75 lbs of force compressing the device if she was lying on her chest. The ultimate static loads exceeded 75 lbs.

The resulting endurance load levels for the subject Mentor silicone gel breast implants were 20-30 lbs. As expected, all fatigue failure modes were small radial tears. As a note, the endurance load level for Mentor's smooth and textured saline-filled breast implants was 10 lbs.

2. Analysis of Cyclic Fatigue Testing of Mentor Implants

This report involved a new analysis of the raw data collected in the fatigue testing report in item 1 above, as well as newly presented physical property test results. No new data were actually collected. Refer above for a summary of the samples tested, the test methodology, and the static and fatigue results. Below is a summary of the newly presented physical property test results, followed by the new analyses of that testing for the Smooth Round Moderate Profile and Siltex Round Moderate Profile devices.

Mentor evaluated the existing physical property data for devices subjected to cyclic loading. These data included ultimate tensile strength and elongation; stress at 100%, 200%, and 300% elongation; rupture energy, and Young's modulus. Samples from 2-3 devices were tested prior to and following cyclic testing. Mentor stated that the testing was performed on devices subjected up to 10M cycles, which is the equivalent to ≈1 year of physical activity. The results showed no significant change in material properties following cyclic testing. *Mentor stated that this testing indicated that, following the equivalent of 1 year of cyclic fatigue, no changes were observed in physical properties of the shell and gel components. However, this does not imply that longer in-vivo implant lifetimes would not result in degradation of physical properties leading to failure.*

In terms of analyzing the cyclic fatigue results, Mentor stated that the cyclic fatigue data can be used to estimate a fatigue lifetime for devices in-vivo. The Basquin equation[25] is defined as: $\sigma_a = bN^c$, where σ_a = Basquin Stress, b and c = Constants, and N = Number of Cycles. The Basquin equation expresses a relationship between fatigue cycles-to-failure data and fatigue lifetime. However, Mentor stated that the Basquin equation is used for completely reversed cyclic loading, which is not the case for this testing. The Gerber equation[26] is defined as $\sigma_{ga} = S_A [1-(\sigma_m/S_U)^2]$, where σ_{ga} = Stress Amplitude, S_A = Fatigue Lifetime Parameter, σ_m = Mean Stress, and S_U = Ultimate Tensile Strength. The Gerber equation expresses a relationship between mean stress and stress amplitude and fatigue lifetime. Mentor substituted the Gerber stress amplitude

σ_{ga} with the Basquin stress σ_a to develop the Basquin-Gerber relation - $S_a = bN^c$. Parameters b and c for this equation are obtained by applying a best fit straight line to a log-log plot of the load or stress amplitude versus the number of cycles to failure. This estimation was performed as described in the steps below.

Mentor first calculated the load amplitudes, maximum stresses, and stress amplitudes. To determine the maximum stresses, Mentor calculated the tensile stress at the radius, which is considered the location of highest tensile stress during cycling and the parameter most likely to control fatigue failure. The stress amplitudes were calculated as the tensile stress at the radius at maximum compressive load minus the tensile stress at the radius at minimum compressive load of 10 lbs. The load and stress amplitudes vs. number of cycles to failure (N) were plotted. Mentor used the Basquin-Gerber relationship, $S_a = bN^c$, as a best fit to the data and then determined the b and c parameters.

For the activities of walking/jogging/running, lying face down (or similar activity), and wrinkling stress, Mentor calculated the estimated corresponding in-vivo stress or load as discussed below.

With regard to the **walking/jogging/running stress**, Mentor stated that the stress was based on F=ma, which is independent of the frequency or differences of the height of motion of the breast seen between walking, jogging, and running. The resulting estimated applied stress amplitudes were --- psi for Siltex and --- psi for smooth devices. Mentor considers this an overestimate because it does not take into consideration support from tissue below and laterally from the ribcage.

With regard to **lying face down**, Mentor estimated the compressive load amplitude to be - lb, which is significantly different than the --- lbs noted for the report above. Mentor stated that the previous calculations were incorrect. Mentor then stated that that the - lbs is based on a 300-lb woman, with 150 lbs for the torso and 75 lbs for the upper half of that torso. Based on a breast implant diameter of ≈3.5", Mentor calculated the area of a breast implant to be 9in^2 and then estimated this to be 5% of her torso area. Based on an estimated torso weight of 100 lbs, Mentor calculated a typical compression load to be 5 lbs through one breast implant when a woman is lying face down.

With regard to **wrinkling**, Mentor estimated the stress amplitude to be --- lbs. Mentor stated that they first estimated a ----- strain based on visual inspections of folds, and then took the corresponding stress of --- psi from the static curves.

Mentor then used the Basquin-Gerber relationship, $S_a = bN^c$, again to determine lifetime estimate (N) for each of the 3 activities above. The resulting stress and load amplitudes determined above (i.e., ---------- psi) were inserted as the S_a values. The b and c parameters used were those pre-determined. The resulting estimated lifetime values (N) were then calculated. Mentor then determined the fraction of lifetime that was expended per year: (1) by walking/jogging/running with absent/negligible shell wrinkling; (2) by lying face down; and (3) by walking/jogging/running with shell wrinkling. The expenditures per year were based on Mentor's estimated frequency of the activities. The table below summarizes this information.

Activity	Device Type	Estimated In-Vivo Load/Stress	Estimated Lifetime (N)	Estimated Frequency of Activity	Estimated Expenditure of Lifetim----ear
Walking/jogging/ running	Siltex	--- psi	--------- ---	walking/jogging/running for 10 hours/day every day at 1 pace/sec or runs 5 hours/day at 2 paces/second for a total of $1.31x10^7$ paces/year	--------- --
	Smooth	--- psi	--------- ---		--------- --
Lying face down (or similar actions)	Siltex	- lbs	--------- ---	10^3 times/day for a total of $3.66x10^5$ cycles/year	--------- --
	Smooth		--------- -		--------- --
Shell wrinkling	Siltex	--- psi	--------- 8	Not calculated	Not calculated
	Smooth		--------- -		
Walking/jogging/ running with shell wrinkling	Siltex				------- ------- ---- ---- ------ -
	Smooth				------- ------- ---- ---- ------ -

Lying face down was found to have a negligible impact on fatigue life. Based on a fatigue life dominated by walking/jogging/running with shell wrinkling, Mentor estimated the fatigue lifetimes as --- years for Siltex devices and ---- years for smooth devices.

In conclusion, Mentor stated that because these failures will result from long-term fatigue that is not confounded by other failure modes, they believe that this cyclic fatigue analysis provides a very rough estimate for in-vivo device life. However, Mentor admitted that, even with conservative values for stress level and frequency which should have lowered the device life, they believe that the estimate of --- years is excessively high. To assess the relative numbers of devices that will survive long-term in the total implanted population, Mentor stated that they need to address both overt and silent ruptures. From their complaint database analysis, Mentor cited the number of overt ruptures through about --- years as ≈---- Mentor then cited the estimate silent rupture rate derived from the unpublished ---------- study of ----- at --- years, which was then extrapolated to a failure rate of ≈----- at --- years. Mentor added the percentage of overt and silent ruptures at 15 years to obtain a very rough estimate of total failures at 15 years is 16%. If Mentor makes the simple assumption that this rate continues unchanged, then it would require 47 years for half of the originally implanted devices to fail. If the rate increases over time, as Mentor projects that it will during the second mode of the bimodal distribution, then they estimate that the actual median life of the devices rupturing from pure cyclic fatigue would lie somewhere between ≈--- and --- years. *Although Mentor provided a reasonable approach at estimating the fatigue life of their device, FDA believes that, given the assumptions used for their estimation and the lack of pure cyclic failure observed in their testing, the accuracy of this estimate is unknown.*

Mentor provided additional information regarding this fatigue testing. Mentor stated that predicting device life based upon cyclic fatigue date requires 3 elements: (1) cyclic fatigue tests conducted at constant stress at the areas that are most vulnerable to failure (i.e., radius) and carried out to device failure; (2) a relationship (Basquin-Gerber equation) that provides a

correlation between the laboratory fatigue data and in-vivo device life; and (3) model assumptions of in-vivo conditions that are assumed to lead to failure. The specific in-vivo model that Mentor selected for use was conservative and was based upon observable activities of a patient (walking or jogging at a given frequency and with the resultant stress) intended to produce the shortest device life. Mentor recognizes the possibility that there might be some other model parameters (e.g., un-observable such as normal flexing of the pectoralis major muscle) that could lead to a shorter device life. However, Mentor was unable to develop a reasonable model. Plus, they expect the influence of fatigue on the device life to be minimal, if even measurable. Bottom line is that Mentor could not identify any practical model conditions that are more challenging than the ones that they chose and that produced the average device life of 60 years.

Accordingly, Mentor estimated the very lowest possible median life of --- years and assumed that the failure rate at --- years (----- failures in --- years) would continue and be constant to provide an upper limit of a median life of --- years. These limiting extrapolations were presented to emphasize that, even when the absolute worst case generalized assumptions are applied, the median life of these devices is substantial. In conclusion, Mentor believes that their cyclic fatigue testing provides a sound in-vitro simulation in predicating in-vivo cycles to failure.

F. GEL COHESION DATA

Mentor evaluated gel cohesivity through 3 different tests: gel cohesion; penetrometer; and gel rheology.

1. Gel Cohesion

Gel cohesion testing assesses the tendency of a gel to resist flow. Gel cohesion testing was performed as per ASTM F703 (cone/pendant method). Mentor used 98-105gms of gel from the following final sterilized implants: 250cc Smooth Round Moderate; 800cc Smooth Round Moderate; and 450cc Siltex Round High Profile. All samples were allowed to settle for 10 minutes prior to release of the bottom of the cone fixture. Then the test was conducted for 30 minutes as per ASTM F703. Five sets of 20 samples (or 100 samples) were tested. 4 of 5 sets (or 80 samples) showed no measurable pendant length. One set of 20 samples showed an average pendant length of 0.1cm. All samples passed the ASTM F703 specification of <4.5cm.

2. Gel Penetration

Gel penetration testing assesses the stiffness of a gel, which provides an indirect measure of a gel's crosslink density. The gel was placed into a jar. A flat weighted plunger/head (14.5 gms and 1" diameter) was put onto the surface of the gel. After 5 seconds, the depth of penetration of the plunger into the gel was measured. Each of the 7 jar samples contained ≥200g of gel. The Mentor specification for cured gel is -------- penetrometer units. Of the 7 samples tested, the average penetrometer reading was ----- penetrometer units (range of ------- gel penetrometer units). All samples passed Mentor's internal specification.

3. Gel Rheology

Gel rheology testing further characterizes the cohesion of a gel and the extent of crosslinking of a gel. Cohesion is related to the degree to which gel matrix constituents stick together tightly. The extent of crosslinking is related to manufacturing process control and reproducibility. The rheometer twists the sample and measures the resultant load or torque. The frequency of the twisting was controlled and related to shear rate or tearing of the gel. Approximately 1g of the finished sterilized gel from the Siltex Round Moderate Profile device was used. In terms of results, the crossover modulus (G'/G") was directly proportional to the extent of crosslinking. The average crossover modulus was ------ dyn/cm^2 (n=-). The complex modulus (G*) and complex viscosity (η*) were directly proportional to the gel cohesiveness. The average complex modulus (G*) was ≈------ dyn/cm^2, and the average complex viscosity (η*) was ≈-----

In summary, Mentor provided adequate gel cohesion testing as per ASTM F703 and gel penetration testing to address gel cohesivity, as a whole, and to support the PMA. However, it should be noted that the correlation between this testing and long-term clinical performance is not understood.

G. GEL BLEED DATA

In their original PMA submission, Mentor provided ASTM F703 testing and a gel loss analysis. The ASTM F703 test method was not developed to mimic in-vivo conditions but, instead, to accelerate the bleed diffusion process to compare various smooth implant designs. In addition, FDA did not believe that Mentor's gel loss analysis adequately addressed gel bleed.

In the 4/14/04 major deficiency letter, FDA asked Mentor to provide new gel bleed testing that mimics the in-vivo environment in order to identity the gel bleed constituents (including the platinum species (or other catalysts)), the rate that the gel constituents bleed out, and how that rate changes over time. FDA believes that this information is needed to fully characterize the device and its interaction with the body over its expected lifetime. It is also needed so that women may be informed of the identity and quantity of chemical constituents that leak out of an intact implant.

In their August 2004 submission, Mentor provided new gel bleed testing, which is summarized below. Mentor also provided an updated gel loss analysis. All testing provided by Mentor to address gel bleed is summarized below.

1. ASTM F703 Gel Bleed Testing

Gel bleed testing was performed as described in ASTM F703. Testing was completed on finished, sterilized Smooth Moderate Profile implants (350cc;------" average thickness), which was considered representative of their silicone gel product lin------- per ASTM F703, the samples were conditioned in an oven at 110°F. At weekly intervals, the test and control samples (n=3 each) were allowed to equilibriate at room temperature and then weight gain measurements were taken. ASTM F703 describes an 8-week study; however, Mentor continued their testing out to 15 weeks. The results were as follows:

	Results at 1 week	**Results at 8 weeks**	**Results at 15 weeks**
Average Weight Gain (W_g = g/cm^2)	--------	--------	--------
Average Weight Gain Rate (R_g = g/cm^2/week)	--------	--------	--------

As stated above, the ASTM F703 test method was not developed to mimic in-vivo conditions but, instead, to accelerate the bleed diffusion process to in order to allow a comparison of various smooth implant designs. Thus, the correlation between this ASTM F703 testing and long-term clinical performance cannot be made, nor is it intended to be made.

FDA recommends that sponsors provide gel bleed testing that mimics in-vivo conditions. This deficiency was conveyed to Mentor in the 4/14/04 major deficiency letter. The testing described below was submitted in response to the 4/14/04 major deficiency letter.

2. Gel Loss Analysis Study

In the original PMA submission, Mentor provided a gel loss analysis study report on intact explants. The purpose of the study was to determine the rate of gel loss over in-vivo time from intact (and with no abnormalities), explanted Low Bleed Gel devices from Mentor's Product Evaluation (PE) database since 9/12/00. Mentor randomly selected data for --- explants with no pre-existing knowledge of the weights recorded in the database.

Subsequently, Mentor discovered that some of the devices presented in the original report may have been inaccurately weighed at the time the data were entered into the PE database. Thus, in their August 2004 submission, Mentor provided an updated study report that included --- (of the original ---- re-weighed devices.

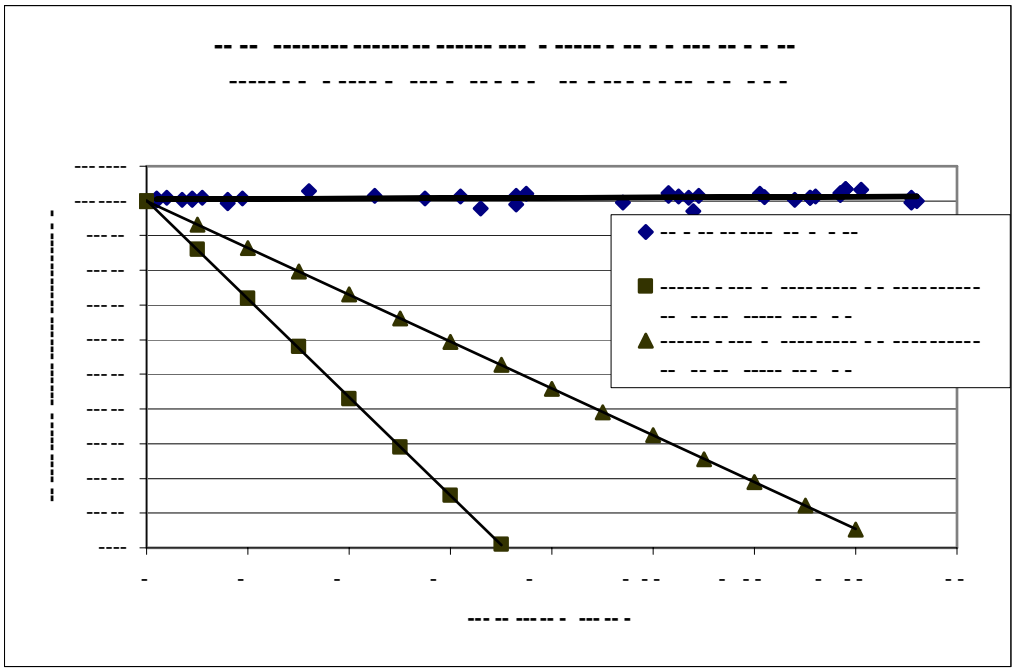
Device weight at the time of gel fill is known within a specified range for a given device size. Mentor calculated a **%** implant weight at explantation by dividing the implant weight at explantation by the nominal specification weight for that device size. However, for a worst case presentation, Mentor also calculated the % implant weight at explantation using the minimum and maximum weight specifications. The results were as follows:

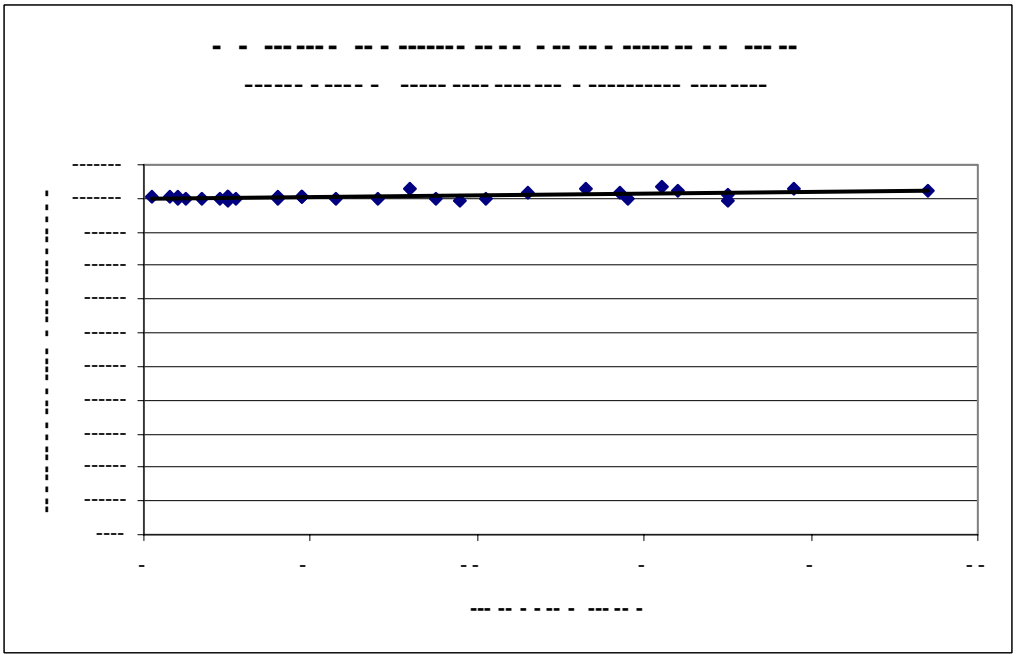
% Weight at explantation as compared to preimplantation	**--- Smooth (0.2-15.2 years)**	**--- Siltex (0.1-9.4 years)**
	Ave (Range)	**Ave (Range)**
% implant weight (nominal weight spec.)	----------	----------
% implant weight (minimum weight spec.)	----------	----------
% implant weight (maximum weight spec.)	----------	----------

No Siltex implants were outside of the fill weight specifications; however, 4 smooth implants were (2 above and 2 below).

Mentor then theoretically calculated the in-vitro gel bleed for a 100cc and 800cc device based on their actual ASTM F703 gel bleed testing. Based on these theoretical calculations for the in-vitro testing, one should expect a 100cc device to lose all of its gel in ≈7 years and an 800cc device to lose all its gel in ≈15 years. This supports Mentor's contention that the ASTM F703 is an accelerated gel bleed test methodology.

Figures 1 (smooth) and 2 (Siltex) below are the best-fit curves based on comparisons to the pre-implantation nominal weights for the --- devices. Figure 1 also includes the theoretical curves based on the ASTM F703 testing. The curves show minimal gel weight loss over a period of --- years for smooth devices and a period of --- years for Siltex devices.





The curves reflect the % implant weights based on pre-implantation nominal weight specifications. The trend line (i.e., best-fit curve) for the smooth devices is essentially horizontal right above the 100% mark, indicating that there was little gel loss from these implants after --- to ----- years of implantation.

The trend line for the Siltex devices is also essentially horizontal right above the 100% mark, with only a very slight increase starting at---- years of implantation. Mentor stated that, while it could possibly be explained by the device absorbing material from the in-vivo surroundings, they would perform additional chemical analysis of explanted devices to see if this was the case.

Mentor, rather, believes that the slight increase in % weight may be due to a change in the filling specification for these devices in 2001. The filling tolerance was appreciably narrowed by ---- ----- for Round Moderate Profile devices, which are the majority of those covered by this report. Thus, the nominal fill value they chose could involve a greater error than for those devices manufactured ≥2001. It should also be noted that the Siltex range was consistently tighter than that for the smooth implants.

The smooth and Siltex devices showed little change in weight over time. Mentor stated that it is not likely that the lack of weight change was based on the replacement of the gel filler by materials from the body. This is because, if appreciable amounts of gel were replaced by materials entering the device and mixing with the gel filler, then one would expect to see noticeable change in the consistency and appearance of the explanted gels. These changes were not seen with intact explants except for a slight yellowing of the gel with some older implants. In addition, Mentor stated that this analysis supports their belief that gel extractable compounds have low solubility in water and, therefore, collect on the surface of the device in-vivo. This would theoretically slow and eventually stop the gel bleed if the compounds are not removed from the device surface in-vivo.

To further support their gel loss analysis, Mentor referenced two other studies. For the **first** study, Mentor stated that they measured the weight of an unimplanted Mentor smooth and 3 unimplanted textured control devices stored on a shelf at room temperature for at least - years. Based upon their measured weights, when taken from the packages and their finished device weight specification, the devices were ---------- of their nominal specification weights. These values were within the range of those seen with the explanted devices in the gel loss analysis above.

For the **second** study, Mentor assessed the potential for infusion of body fluids into device by analyzing - explanted devices ----------in-vivo years) for water, protein, and lipid content. The Karl-Fischer Method (ASTM E203) was used for quantitation of moisture. Soxhlet extraction procedure was used separate the protein from fat and the extractable gel materials. Once separated, HCl was used to release the protein from silicone matrices and hydrolyze the protein to amino acids. HPLC was used to detect and quantitate amino acids. The determination of fat in the extractables was accomplished by FTIR analysis. The results showed that, at most, the equivalent of ---------- of a gram of biological material (i.e., water, protein, fat) would be present in an ------- device. The moisture content values were ≈------ ppm for the shell and <------ ppm for the gel. The protein content values were ------ ppm for the shell and gel. The fat content values were <---- ppm for the smooth shell,------- ppm for the Siltex shell, and ------ ppm for the gel.

Based on the findings from these two additional studies (i.e., (1) unimplanted control data with same weight range and (2) data showing minimal water, protein, or lipids entering the device), Mentor concluded that the lack of noticeable device weight change over the 9-15 years of implantation presented in the gel loss analysis report was due to the relative lack of gel bleed from the device.

FDA considers this test to be of limited value because the explanted samples were not kept under controlled conditions, either while implanted in the body (which is not possible) or after explantation. Exposure of the samples to different in-vivo or environmental conditions may influence the potential weight gain or loss. Furthermore, this test only provides an overall gel bleed rate and does not identify and quantify the rate of bleed for all gel bleed constituents.

3. Gel Bleed Study

FDA recommends that sponsors provide information in order to identity the gel bleed constituents (including the platinum species (or other catalysts)), the rate that the gel constituents bleed out, and how that rate changes over time. These data are needed in order to provide complete labeling information for women who receive these implants. In response to the 4/14/04 major deficiency letter, Mentor provided new gel bleed testing, as described below.

Test Method –A new test method was developed by Mentor, which was designed to mimic in-vivo exposure to silicone gel-filled breast implants. Mentor Smooth Round Moderate Profile Gel-Filled Implants (125cc; n=-) were incubated in 225ml ---------- at 37°C, with gentle stirring to ensure adequate mixing, and in the presence of ---------- to minimize microbial growth. At timepoints (n=---) ranging from 1 to 120 days, 20ml aliquots were withdrawn for analysis of low molecular weight (LMW) silicones (D3-D6, and D9; MW<1500) and platinum. Fresh ------- - -------- (20ml) was added after each test sample was withdrawn.

As a note, Mentor performed preliminary experiments to determine the solubility of target LMW silicones and platinum-siloxane complex in ---------- and to estimate the maximum amounts (---- µg LMW silicones; ------ µg platinum) of the analytes that the ---------- medium could hold (i.e., solubility limits did not restrict diffusion of these materials out of the implants in this test system). Solubility was determined using ASTM E1148.

LMW silicones were analyzed by gas chromatography/mass spectrometry (GC/MS) after extraction of serum samples with methylene chloride. The sensitivity was <0.01 ppm for each analyte. Platinum levels were determined by inductively coupled plasma-mass spectrometry. The sensitivity for platinum was 2 ppb.

Results – Mentor stated that the diffusion of measured constituents ceased by ---- days. D4, D5, D6, and platinum exhibited measurable diffusion into the serum over a period of ---- days. The maximum cumulative amount of LMW silicones was --- µg after --- days. Levels of D5 (------) were the highest. ------- corresponds to 1.2% of total methylene chloride extractable LMW silicones that could have leaked from gel filler into --------- serum. Variability in the LMW silicone analysis was likely due to volatility and other factors discussed. The release rate of LMW silicones could not be determined accurately, because the bleed levels were very low (close to background) and did not show a consistent time-dependent pattern

The maximum cumulative amount of platinum was --- µg after --- days, corresponding to ------ of total platinum that could have leaked from gel filler into - - ------ serum. No additional platinum was detected after that time. The platinum results were less variable than LMW silicone results, because the platinum-siloxane complexes are less volatile. The release of

platinum was time-dependent for the first --- days with a release rate of ≈[redacted]/day of surface area for the 125cc implants tested.

Mentor stated that they did not detect any higher oligosiloxanes that diffused out in the gel bleed material.

FDA considers Mentor's new testing to be of limited value based on the following outstanding issues:

- *To justify that the test methodology mimics in-vivo conditions, Mentor did not explain why diffusion would cease in-vivo by day 120, as it was observed in the in-vitro experiment. In addition, Mentor did not discuss the relationship between implant size and the volume of --------- serum medium used for this gel bleed testing.*

- *Mentor did not provide the rate of diffusion for each gel bleed constituent.*

- *The LMW siloxanes were analyzed by GC analysis without using headspace technique. It is not clear whether any correction was applied to the quantification of low molecular weight oligosiloxanes due to their high volatile character.*

H. SHELF LIFE DATA

Shelf life testing for breast implants is comprised of device and package testing. The device testing includes shell tensile set, shell/patch joint strength, shell ultimate elongation, shell break force, and gel cohesion. The package testing consists of inner/outer thermoform dye penetration and inner/outer lid packaging seal peel testing.

Mentor provided a combination of accelerated and real-time testing on their silicone gel product. This included real-time testing on devices and package that were ⩾5 years old taken from numerous lots that were in inventory.

With their combination of data, Mentor was able to support their 5-year shelf life for their silicone gel product labeling and to validate their accelerated test model out to 5 years.

I. CORE STUDY CLINICAL DATA

The Core Study used to support this PMA was conducted under IDE----------. The Core Study is a 10-year study designed to evaluate the safety and effectiveness of a subset of the implants under PMA review (i.e., Smooth Moderate Profile and Siltex Moderate Profile) for the indications of augmentation, reconstruction, and revision patients. The protocol was approved for 1000 patients (550 augmentation, 250 reconstruction, and 200 revision) at 60 sites with evaluation timepoints at preoperative, operative, 6 months, and 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 years. Quality of Life (QoL) assessment timepoints are preoperative, 1, 2, 4, 6, 8, and 10 years. The approved protocol also included a cohort of 405 patients who receives MRIs to evaluate silent rupture at 1, 2, 4, 6, 8, and 10 years.

The first patient was enrolled in----------on 9/12/00, and the last patient was enrolled on 11/28/01. The date of database closure was 7/15/04. There were 1,007 (551 augmentation, 251 reconstruction, and 205 revision) patients enrolled by 40 primary investigators at 49 sites and involving a total of 1,896 implants. A subset of 420 patients was included in the MRI cohort and has undergone MRI evaluation at years 1 and 2 at the time of PMA submission. Although Mentor is seeking approval for 6 styles, only the Smooth and Siltex Moderate Profiles were studied in----------

Refer to Section J (**Rupture Rate and Health Consequences**) below for a detailed description of the information provided to address rupture rate and rate over time, as well as the health consequences of rupture, as it relates to the Core Study and other supplemental sources of clinical data.

It is important to note that the clinical data in this Panel review memo are shown with data separately for primary augmentation, primary reconstruction, and revision indications. FDA believes that it is important to consider the data for revision patients within the context of the augmentation or reconstruction patient populations, which are the original indications for which patients receive breast implants. For example, when considering the safety for augmentation patients, 15 (3%) of 551 patients had revision surgery (i.e., device removal with study device replacement) through 3 years, converting their risk to that of revision patients, who have different risks and benefits to consider. Therefore, the clinical data collected on revision patients should be considered in your determination of whether the data demonstrates a reasonable assurance of safety of the device for augmentation and reconstruction patients (question 5 of the Panel questions provided in Tab 2 of your Panel package).

1. Patient Accounting

The table below summarizes the revised 3-year patient accounting data for the Core Study for each of the indications. Approximately 26% of the patients are not yet due/overdue for their 3-year follow-up visit. Therefore, it is important to note that all clinical data below are based on a partial 3-year follow-up data. The 2-year follow-up rates (based on complete data) and 3-year follow-up rates (based on partial data) are similar.

Patient Accounting through 3 Years	Augmentation	Reconstruction	Revision
Number enrolled	1110 devices in 551 patients	410 devices in 252 patients	386 devices in 204 patients
Theoretically due[1]	439	144	158
Deaths	0	9*	0
Patients with all devices removed without replacement[2]	7	8	7
Patients with all devices removed and replaced with study device	15	18	15
Expected[3]	432	127	151
Actual (Patients with complete follow-up)	404	121	140
Lost-to-follow-up	9	1	3
Percent Follow-up (Actual/Expected)	94%	95%	93%

[1] Patients who would have been examined according to implant date and follow-up schedules.
[2] Although not collected, some of these patients may have been reimplanted with a non-study device after discontinuation from this study.
[3] Patients theoretically due minus (1) deaths and (2) patients with all devices removed without replacement.
*All 9 deaths were due to breast cancer.

2. Demographics and Implant and Operative Characteristics

The table below summarizes the **patient demographic** information, stratified by indication.

Patient Demographics	Augmentation N = 551 Patients	Reconstruction N=251 Patients	Revision N=205 Patients
Median age (range) in years	34 (18-65)	46 (18-79)	44 (20-72)
Number (%) Caucasian	482 (87%)	231 (92%)	190 (93%)
Median weight (range) in pounds	125 (85-200)	139 (98-280)	130 (85-198)

The table below summarizes the **implant and operative characteristics**, stratified by indication.

Characteristic		Augmentation N = 1100 Implants	Reconstruction N = 410 Implants	Revision N = 386 Implants
Implant Surface	Smooth	767 (70%)	171 (42%)	257 (67%)
	Textured	333 (30%)	239 (58%)	129 (33%)
Surgical approach	Inframammary	652 (59%)	79 (19%)	236 (61%)
	Periareolar	256 (23%)	86 (21%)	75 (19%)
	Transaxillary	182 (17%)	0	6 (2%)
	Mastectomy Scar	0	232 (57%)	51 (13%)
	Mastopexy	6 (<1%)	12 (3%)	8 (2%)
	Other[1]	4 (<1%)	1 (<1%)	10 (3%)
	Missing	0	0	0
Implant Location	Submuscular	456 (42%)	251 (61%)	207 (54%)
	Subglandular	372 (34%)	42 (10%)	123 (32%)
	Subpectoral	272 (25%)	107 (26%)	56 (15%)
	Other[2]	0	9 (2%)	0
	Missing	0	1 (0.2%)	0

Characteristic		Augmentation N = 1100 Implants	Reconstruction N = 410 Implants	Revision N = 386 Implants
Incision size	Median (range)	4 (2-16) cm	6 (2-28) cm	5 (2-20) cm
Pocket irrigation	Saline only	461 (42%)	135 (33%)	153 (40%)
	Steroid	67 (6%)	55 (13%)	24 (6%)
	Antibiotic	700 (64%)	286 (70%)	236 (61%)
	Drug	114 (10%)	62 (15%)	36 (9%)
	Betadine	8 (<1%)	46 (11%)	5 (1%)
	Betadine & saline	112 (10%)	1 (<1%)	39 (10%)
	Anesthetic	72 (7%)	20 (5%)	13 (3%)
	Other[3]	2 (<1%)	2 (<1%)	2 (<1%)

[1]Other surgical approaches include periareolar-inframammary (1) and vertical (3) for augmentation; lateral aspect latissimus flap (1) for reconstruction; augmentation incision scar (3), biopsy scar (1), periareolar and inframammary (2), thru old vertical scar (2), wise incision (2) for revision.

[2]Other implant locations include above tram flap muscle (1), beneath flap (1), subcutaneous (2), submastectomy flap (1), Submuscular > latissimus dorsi flap (2), submuscular and subpectoral and sublatissimus (1), under latissimus dorsi (1) for reconstruction.

[3]Other pocket irrigations include saline and hibiclens (2) for augmentation; betadine and then rinsed out with gentamycin (2) for reconstruction; and thrombostat (2) for revision.

3. KM Risk Rates of Complications

The tables below compare 2 and 3-year, by-patient, cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of complications with ≥1% rate for the augmentation, reconstruction and revision indications separately. 187 augmentation, 102 reconstruction, and 87 revision patients experienced at least one complication or reoperation through 3 years. Please refer to Section J (**Rupture Rate and Health Consequences**) for information specific to implant rupture.

By Patient, Cumulative KM Risk Rates of Complications with ≥1% Rate through 2 and 3 Years[1]		
Complication	**Augmentation N=551**	
	2-Year Rate (95% CI)	**3-Year Rate (95% CI)**
Breast mass	2.1% (0.9, 3.4)	2.4% (1.0, 3.7)
Breast pain	1.7% (0.6, 2.8)	1.7% (0.6, 2.8)
Breast sensation changes	2.2% (1.0, 3.4)	2.2% (1.0, 3.4)
Capsular contracture III/IV	7.8% (5.5, 10.0)	8.2% (5.9, 10.6)
Hematoma	2.6% (1.2, 3.9)	2.6% (1.2, 3.9)
Hypertrophic scarring	6.3% (4.2, 8.3)	6.3% (4.2, 8.3)
Implant removal w/ or w/o replacement	3.7% (2.1, 5.3)	5.1% (3.2, 7.1)
Infection	1.5% (0.5, 2.5)	1.5% (0.5, 2.5)
Miscarriage	1.1% (0.2, 2.0)	1.4% (0.4, 2.4)
Nipple sensation changes	9.3% (6.9, 11.8)	10.8% (8.1, 13.4)
Ptosis	1.9% (0.7, 3.1)	2.2% (0.9, 3.4)
Reoperation	12.4% (10.0, 15.1)	15.0% (11.9, 18.0)
Rupture	0%	0.5% (0.0, 1.5)

[1]Complications are listed if the rate is ≥1%; rupture also included for completeness. Excludes mild occurrences of asymmetry, breast pain, calcification, position change, nipple sensation changes, nipple complications, and wrinkling. The reoperation rate also excludes planned secondary surgeries and reoperations.

By Patient, Cumulative KM Risk Rates of Complications with ≥1% Rate through 2 and 3 Years[1]		
Complication	**Reconstruction N=251**	
	2-Year Rate (95% CI)	**3-Year Rate (95% CI)**
Asymmetry	4.5% (1.9, 7.1)	7.1% (3.2, 11.1)
Breast mass	3.0% (0.8, 5.3)	3.9% (1.1, 6.6)
Breast pain	1.7% (0.0, 0.4)	1.7% (0.0, 0.4)
Capsular contracture III/IV	7.2% (3.9, 10.5)	8.8% (4.9, 12.7)
Hematoma	1.5% (0.0, 3.3)	1.5% (0.0, 3.3)
Hypertrophic scarring	5.6% (0.3, 8.6)	6.4% (3.0, 9.8)
Implant extrusion	1.2% (0.0, 2.6)	1.2% (0.0, 2.6)
Implant malposition/ displacement	1.7% (0.0, 3.3)	1.7% (0.0, 3.3)
Implant removal w/ or w/o replacement	11.8% (7.8, 15.8)	13.3% (8.8, 17.8)
Infection	5.3% (2.5, 8.2)	5.3% (2.5, 8.1)
Metastatic disease	1.9% (0.0, 3.7)	1.9% (0.0, 3.7)
Necrosis	0.4% (0.0, 1.2)	1.2% (0.0, 2.0)
Nipple sensation changes	1.7% (0.0, 3.3)	3.1% (0, 6.3)
Ptosis	2.5% (0.3, 4.7)	6.9% (2, 11.8)
Recurrent breast cancer	1.7% (0.0, 3.4)	1.7% (0.0, 3.4)
Reoperation	25.4% (20.1, 31.0)	26.3% (21.7, 31.9)
Rupture	0.8% (0.0, 2.2)	0.8% (0,0, 2.2)
Seroma	4.9% (2.2, 7.6)	4.9% (2.2, 7.6)
Wrinkling	2.0% (0.3, 3.8)	2.8% (0.1, 5.1)

[1]Complications are listed if the rate is ≥1%; rupture also included for completeness. Excludes mild occurrences of asymmetry, breast pain, calcification, position change, nipple sensation changes, nipple complications, and wrinkling. The reoperation rate also excludes planned secondary surgeries and reoperations.

By Patient, Cumulative KM Risk Rates of Complications with ≥1% Rate through 2 and 3 Years[1]		
Complication	**Revision N=205**	
	2-Year Rate (95% CI)	**3-Year Rate (95% CI)**
Asymmetry	2.0% (0.1, 4.0)	2.7% (0.3, 5.1)
Breast mass	4.6% (1.6, 7.5)	5.8% (2.5, 9.1)
Breast pain	2.0% (0.1, 4.0)	2.0% (0.1, 4.0)
Breast sensation changes	1.5% (0.0, 3.2)	2.1% (0.1, 4.2)
Capsular contracture III/IV	16.5% (11.3, 21.7)	17.2% (11.9, 22.4)
Delayed wound healing	2.0% (0.1, 3.9)	2.0% (0.1, 3.9)
Granuloma	1.0% (0.0, 2.3)	1.0% (0, 2.3)
Hematoma	3.0% (0.6, 5.3)	3.0% (0.6, 5.3)
Hypertrophic scarring	6.0% (2.7, 9.3)	6.0% (2.7, 9.3)
Implant extrusion	1.5% (0.0, 3.1)	1.5% (0.0, 3.1)
Implant malposition/ displacement	2.5% (0.3, 4.7)	2.5% (0.3, 4.7)
Implant removal w/ or w/o replacement	10.0% (5.9, 14.2)	13.3% (8.4, 18.2)
Infection	1.0% (0.0, 2.4)	1.0% (0.0, 2.4)
Inflammation	1.5% (0.0, 3.2)	1.5% (0.0, 3.2)
New diagnosis of rheumatic disease	1.0% (0.0, 2.4)	1.0% (0.0, 2.4)
Nipple sensation changes	8.0% (4.2, 11.8)	8.6% (4.7, 12.6)
Ptosis	2.2% (0.06, 4.3)	2.2% (0.06, 4.3)
Reoperation	21.3% (15.6, 26.9)	26.3% (20.0, 32.6)
Rupture	3.6% (0.0, 7.5)	4.8% (0.2, 9.3)
Seroma	2.0% (0.1, 3.9)	2.0% (0.1, 3.9)
Wrinkling	2.0% (0.1, 4.0)	2.0% (0.1, 4.0)

[1]Complications are listed if the rate is ≥1%; rupture also included for completeness. Excludes mild occurrences of asymmetry, breast pain, calcification, position change, nipple sensation changes, nipple complications, and wrinkling. The reoperation rate also excludes planned secondary surgeries and reoperations.

4. Overview of Reoperations and Additional Surgical Procedures

The table below summarizes the number of patients, implants, reoperations, and additional surgical procedures, per indication, for the Core Study through 3 years. Note that these reoperations relate to reoperations and additional procedures which were not planned by the surgeon.

Indication	**Number of**			
	Reoperations	**Additional Surgical Procedures**	**Patients**	**Implants**
Augmentation	98	160	79	115
Reconstruction	78	139	64	82
Revision	71	141	51	78
Total	329	440	194	275

5. Reasons for Reoperation

There were 79 augmentation patients who had 98 reoperations. There were 64 reconstruction patients who had 78 reoperations. There were 51 revision patients who had 71 reoperations. The table below summarizes all the reasons reported by the physician for each reoperation, stratified by indication, through 3 years. Because some surgeons reported multiple reasons for needing a reoperation, the percentages exceed 100%. Note that these reoperations relate to reoperations and additional procedures which were not planned by the surgeon.

Reasons for Reoperation through 3 Years[1]			
Reasons	**Augmentation N=98 Reops**	**Reconstruction N=78 Reops**	**Revision N=71 Reops**
Asymmetry	5 (5.1%)	20 (25.6%)	3 (4.2%)
Breast mass	4 (4.1%)	9 (11.5%)	6 (8.5%)
Breast pain	2 (2.0%)	1 (1.3%)	0
CC III/IV	43 (43.9%)	10 (12.8%)	28 (39.4%)
Delayed wound healing	1 (1.0%)	0	4 (5.6%)
Extrusion	1 (1.0%)	2 (2.6%)	3 (4.2%)
Hematoma	11 (11.2%)	2 (2.6%)	5 (7.0%)
Hypertrophic scarring	15 (15.3%)	3 (3.8%)	5 (7.0%)
Implant malposition/displacement	3 (3.1%)	11 (14.1%)	3 (4.2%)
Infection	3 (3.1%)	4 (5.1%)	1 (1.4%)
Irritation/inflammation	0	0	1 (1.4%)
Necrosis	2 (2.0%)	0	0
Nipple related (unplanned)	0	2 (2.6%)	2 (2.8%)
Patient request	31 (31.6%)	13 (16.7%)	14 (19.7%)
Ptosis	5 (5.1%)	4 (5.1%)	4 (5.6%)
Seroma	1 (1.0%)	1 (1.3%)	1 (1.4%)
Wrinkling	3 (3.1%)	0	4 (5.6%)
Other	4 (4.1%)	11 (14.1%)	15 (21.1%)
Missing	0	2 (2.6%)	1 (1.4%)

[1]The reoperation rate also excludes planned secondary surgeries and reoperations. Also excludes reoperations with primary reasons of CC II. The percentages add to >100% because, for some reoperations, more than one reason was reported.

6. Types of Additional Surgical Procedures

One or more surgical procedures may be performed on a given breast during a given reoperation. The table below summarizes the types of additional surgical procedures performed during all reoperations, stratified by indication, through 3 years.

Types of Additional Surgical Procedures through 3 Years[1]			
Type	**Augmentation N=160 Procedures**	**Reconstruction N=139 Procedures**	**Revision N=141 Procedures**
Biopsy	4 (2.5%)	10 (7.2%)	10 (7.1%)
Capsulectomy	36 (22.5%)	10 (7.2%)	18 (12.8%)
Capsulorrhaphy	4 (2.5%)	2 (1.4%)	6 (4.3%)
Capsulotomy	17 (10.6%)	14 (10.1%)	17 (12.1%)
Implant pocket revision	2 (1.3%)	6 (4.3%)	0
Implant removal with replacement	24 (15.0%)	23 (16.5%)	21 (14.9%)
Implant removal without replacement	21 (13.1%)	17 (12.2%)	18 (12.8%)
Implant reposition	4 (2.5%)	17 (12.2%)	10 (7.1%)
Incision and drainage	12 (7.5%)	4 (2.9%)	7 (5.0%)
Mastopexy	4 (2.5%)	4 (2.9%)	5 (3.5%)
Nipple related procedure (unplanned)	1 (0.6%)	2 (1.4%)	1 (0.7%)
Revision of wound closure	3 (1.9%)	1 (0.7%)	2 (1.4%)
Scar revision	18 (11.3%)	7 (5.0%)	9 (6.4%)
Skin adjustment	8 (5.0%)	14 (10.1%)	12 (8.5%)
Other	2[2] (1.3%)	8[3] (5.8%)	5[4] (3.5%)

[1]The reoperation rate also excludes planned secondary surgeries and reoperations.
[2]Includes 2 excise breast mass procedures.
[3]Includes 1 breast mass excision, 2 create inframammary fold, 1 flap coverage of expander, 2 removal of nodule on chest wall, and 2 revision of breast/external to pocket procedures.
[4]Includes excision of skin lesion, 1 exploration right breast with evacuation of hematoma, 1 needle aspiration, and 1 open incision to rule out implant rupture procedures.

7. Primary Surgical Procedure for Given Reoperation

The reasons for reoperation table above provides the complete list of reasons. Likewise, the additional surgical procedures table above provides the complete list of procedures performed during the reoperations. In addition to those tables above, FDA believes that providing a one-to-one relationship between these sets of data may be helpful. Accordingly, Mentor identified the primary surgical procedure performed for each reason the reoperation was performed.

The tables below summarize the primary surgical procedure performed for a given reoperation, stratified by indication, through 3 years.

Augmentation: Primary Surgical Procedure for Reoperation through 3 Years		
Primary Reason for Reoperation	**Primary Surgical Procedure[1]**	**# (% of 98 Reops)**
Capsular contracture	Capsule procedures	30 (30.6%)
	Implant removal with or without replacement	5 (5.1%)
Device rupture (suspected)[2]	Implant removal with or without replacement	1 (1.0%)
Extrusion	Revision of wound closure	1 (1.0%)
Healing related	Incision and drainage	12 (12.2%)
	Revision of wound closure	1 (1.0%)
	Scar revision	1 (1.0%)
Infection	Implant removal with or without replacement	2 (2.0%)
	Revision of wound closure	1 (1.0%)
Necrosis	Implant removal with or without replacement	1 (1.0%)
Need for biopsy	Biopsy	2 (2.0%)
	Removal of mass or excess tissue	2 (2.0%)
Pain	Implant removal with or without replacement	1 (1.0%)
Patient request	Implant removal with or without replacement	16 (16.3%)
Tear in capsule	Capsule procedures	1 (1.0%)
Unsatisfactory cosmetic result	Capsule procedures	5 (5.1%)
	Implant removal with or without replacement	1 (1.0%)
	Implant reposition	1 (1.0%)
	Mastopexy	1 (1.0%)
	Other	3 (3.1%)
	Scar revision	10 (10.2%)

[1] Hierarchy: implant removal with and without replacement; capsule procedures; flap procedure; pocket revision; implant reposition; surgical exploration; scar revision; biopsy; incision and drainage; kenalog injection; mastopexy; revision of wound closure; removal of mass or excess tissue; nipple related procedure (unplanned); and other (includes ----- --djustment, Create Inframammary Fold, and Revision of Breast/External to Pocket).

[2] Patient [redacted] had suspected rupture which was found to be intact upon explantation.

Reconstruction: Primary Surgical Procedure for Reoperation through 3 Years		
Primary Reason for Reoperation	**Primary Surgical Procedure[1]**	**# (% of 78 Reops)**
Capsular contracture	Capsule procedures	4 (5.1%)
	Implant removal with or without replacement	4 (5.1%)
Extrusion	Implant removal with or without replacement	2 (2.6%)
Healing related	Implant removal with or without replacement	1 (1.3%)
	Incision and drainage	2 (2.6%)
Infection	Implant removal with or without replacement	2 (2.6%)
	Incision and drainage	2 (2.6%)
Missing	Other	1 (1.3%)
Muscle spasm	Implant removal with or without replacement	1 (1.3%)
Need for biopsy	Biopsy	9 (11.5%)
	Removal of mass or excess tissue	2 (2.6%)
Nipple related (unplanned)	Other	1 (1.3%)
	Scar revision	1 (1.3%)
Pain	Capsule procedures	1 (1.3%)
Patient request	Implant removal with or without replacement	7 (9.0%)
Recurrent breast cancer	Biopsy	1 (1.3%)
	Implant removal with or without replacement	1 (1.3%)
Tight bunilli suture	Revision of wound closure	1 (1.3%)
Unsatisfactory cosmetic result	Capsule procedures	5 (6.4%)
	Implant removal with or without replacement	13 (16.7%)
	Implant reposition	6 (7.7%)
	Mastopexy	3 (3.8%)
	Other	4 (5.1%)
	Pocket revision	1 (1.3%)
	Scar revision	3 (3.8%)

[1] Hierarchy: implant removal with and without replacement; capsule procedures; flap procedure; pocket revision; implant reposition; surgical exploration; scar revision; biopsy; incision and drainage; kenalog injection; mastopexy; revision of wound closure; removal of mass or excess tissue; nipple related procedure (unplanned); and other (includes Skin Adjustment, Create Inframammary Fold, and Revision of Breast/External to Pocket).

Revision: Primary Surgical Procedure for Reoperation through 3 Years		
Primary Reason for Reoperation	**Primary Surgical Procedure[1]**	**# (% of 71 Reops)**
Capsular contracture	Capsule procedures	13 (18.3%)
	Implant removal with or without replacement	6 (8.5%)
Device rupture (suspected)[2]	Implant removal with or without replacement	1 (1.4%)
	Surgical exploration	1 (1.4%)
Extrusion	Implant removal with or without replacement	2 (2.8%)
	Revision of wound closure	1 (1.4%)
Healing related	Incision and drainage	7 (9.9%)
	Other	1 (1.4%)
	Revision of wound closure	1 (1.4%)
	Scar revision	1 (1.4%)
	Surgical exploration	1 (1.4%)
Infection	Implant removal with or without replacement	1 (1.4%)
Need for biopsy	Biopsy	7 (9.9%)
	Implant removal with or without replacement	1 (1.4%)
	Incision and drainage	1 (1.4%)
	Removal of mass or excess tissue	1 (1.4%)
Nipple related (unplanned)	Capsule procedures	1 (1.4%)
Patient request	Implant removal with or without replacement	7 (9.9%)
Pocket tear	Implant removal with or without replacement	1 (1.4%)
Recurrent breast cancer	Biopsy	1 (1.4%)
Symmastia	Capsule procedure	1 (1.4%)
	Implant removal with or without replacement	1 (1.4%)
Unsatisfactory cosmetic result	Capsule procedures	2 (2.8%)
	Implant removal with or without replacement	5 (7.0%)
	Implant reposition	3 (4.2%)
	Other	1 (1.4%)
	Scar revision	2 (2.8%)

[1] Hierarchy: implant removal with and without replacement; capsule procedures; flap procedure; pocket revision; implant reposition; surgical exploration; scar revision; biopsy; incision and drainage; kenalog injection; mastopexy; revision of wound closure; removal of mass or excess tissue; nipple related procedure (unplanned); and other (includes skin adjustment, create Inframammary Fold, and Revision of Breast/External to Pocket).

[2] Patients [redacted] and [redacted] had suspected ruptures which were found to be intact upon explantation or surgical exploration. Patient [redacted] who had confirmed bilateral ruptured implants, is not included in this table because the ruptures were reported after the date of database closure for the 3-year data presented in this table.

8. Reasons for Removal

There were 26 augmentation, 31 reconstruction, and 25 revision patients who underwent device removal. The table below summarizes the reasons for removal, on a by-implant basis, through 3 years. There is no hierarchy because only one reason for a given removal was provided.

Reasons for Removal through 3 Years[1]			
Reasons	**Augmentation N=45 Explants**	**Reconstruction N=40 Explants**	**Revision N=39 Explants**
Asymmetry	0	10 (25.0%)	3 (7.7%)
Breast pain	2 (4.4%)	0	0
CC III/IV	5 (11.1%)	4 (10.0%)	11 (28.2%)
Extrusion	0	2 (5.0%)	2 (5.1%)
Hematoma	0	1 (2.5%)	0
Hypertrophic scarring	0	0	1 (2.6%)
Implant malposition/displacement	0	3 (7.5%)	0
Infection	2 (4.4%)	2 (5.0%)	1 (2.6%)
Necrosis	2 (4.4%)	0	0
Patient request	31 (68.9%)	13 (32.5%)	14 (35.9%)
Wrinkling	1 (2.2%)	0	0
Other[2]	2 (4.4%)	5 (12.5%)	7 (17.9%)

[1]Excludes reoperations for which the only reason for reoperation was staged reconstruction. Also excludes revision patient [redacted] who had confirmed bilateral implant ruptures after the date of database closure for the 3-year data presented in this table.

[2]Includes 1 false positive MRI for rupture and 1 "right explanted so left done also" cases for augmentation; 1 lack of projection, 1 muscle spasm, 1 recurrent breast cancer, and 2 "too large" cases for reconstruction; 1 abnormal mammogram, 2 patient dissatisfied with appearance, 1 pocket tear, 1 suspected rupture found to be intact (patient [redacted], and 2 symmastia cases for revision.

9. Complications following Implant Replacement

Of the 82 patients explanted, 48 patients (15 augmentation, 18 reconstruction, and 15 revision) were reimplanted with a study device through 3 years. Although KM risk rates were provided by Mentor, FDA did not include these data below because of the small sample sizes. However, below is a brief summary of the number of patients per each reported complication. It is important to note that the patient counts cannot be added because a patient may have reported more than one occurrence of a complication.

Of the 15 augmentation patients who underwent implant removal with replacement through 3 years, complications following implant replacement were nipple sensation changes (1 patient), hypertrophic scarring (1 patient), and reoperation (1 patient).

Of the 18 reconstruction patients who underwent implant removal with replacement through 3 years, complications following implant replacement were capsular contracture III/IV (1 patient), extrusion (1 patient), hematoma (2 patients), implant malposition/displacement (1 patient), distortion of breast shape not related to capsular contracture (1 patient), hypertrophic scarring (1 patient), implant removal with replacement (1 patient), infection (2 patients), and reoperation (2 patients).

Of the 15 revision patients who underwent implant removal with replacement through 3 years, complications following implant replacement were capsular contracture III/IV (3 patients), lactation difficulties (1 patient), patient request for removal (1 patient), implant removal without replacement (2 patients), and reoperation (3 patients).

10. Connective Tissue Disease (CTD) Data

Mentor collected CTD signs and symptoms from the patients at baseline and at 1, 2, 4, 6, 8, and 10 years. The CTD signs and symptoms were captured on the "Rheumatology Symptoms" and the "Rheumatological Physical Examination" forms. Rheumatic disease data, confirmed by a rheumatologist, were reported on the "Investigator-Completed Rheumatoid Disease Diagnosis Questionnaire." Therefore, there are 3 forms that collect CTD-related data.

There were a total of 12 referrals to a rheumatologist by the participating plastic surgeons: 8 were augmentation patients, 2 were reconstruction, and 4 were revision patients. There were a total of 6 patients with a new diagnosis of a rheumatologic disease: 3 augmentation; 2 revision; and 1 reconstruction. Three of these patients were in the MRI study, and none had a reported rupture during the study. Other than asymmetry, infection, and low nipple sensitivity, there were no other complications reported in these patients.

The table below summarizes the information pertinent to patients with a new CTD diagnosis.

ID # ----------	CTD diagnosis	CTD Onset	Rupture Status	Adverse Events Reported
[redacted] Aug	Hashimoto's Thyroiditis	17 months (4/02)	No rupture via MRI: 1/02, 11/02	Unacceptable low nipple sensitivity
[redacted] Aug	Seronegative RA	19 months (5/03)	None (No MRI)	Baker III CC (7/02)
[redacted] Aug	Autoimmune hypothyroidism, RA	32 months (6/02)	None (No MRI)	None
[redacted] Rev	Fibromyalgia	12 months (9/02)	No rupture via MRI: (8/03)	None
[redacted] Rev	Pyoderma gangrenosa w/ IBD or Crohn's	12 months (6/02)	None (No MRI)	Breast pain: (8/01) Infection: (7/01)
[redacted] Recon	Fibromyalgia	9 months (7/02)	No rupture via 2 MRIs	Asymmetry: (1/02)

Mentor was asked to compare individual CTD signs and symptoms (CTD S/S) as well as CTD S/S categories pertaining to combined fatigue questions, combined pain, and at least one fatigue and one pain question. The tables below summarize the individual CTD signs and/or symptoms used to define combined fatigue and combined pain.

Rheumatological Symptoms for Combined Fatigue	Rheumatological Physical Examination
Exhaustion	
Fatigue	
Weakness	Muscle weakness (including head lift from supine position against gravity, inability to raise arms, inability to get out of chair)

Rheumatological Symptoms for Combined Pain	Rheumatological Physical Examination
Back pain/stiffness	
Joint pain	Joint Tenderness, Tinels or Phalen's signs
Muscle cramps - Frequent	
Muscle pain - Frequent	Tenderness-insertion of deltoids, Muscle tenderness
Neck pain/stiffness	

In terms of the following symptom categories - skin/appendages, muscle, joint, CNS, gastrointestinal, body as a whole, metabolic/nutritional, hearing/vestibular, respiratory, platelet/bleeding, clotting, cardiovascular, vision - the following categories were the most frequently reported cumulatively through 3 years: CNS for augmentation patients (4.1% cumulative incidence; 10.3% cumulative incidence reported for any category); body as whole for reconstruction (9.6% cumulative incidence; 21.5% cumulative incidence reported for any category); and, body as a whole for revision (2.6% cumulative incidence; 21.3% cumulative incidence reported for any category). Body, as a whole, includes fatigue, weakness, exhaustion, generalized aching, dry eyes, dry mouth, severe chest pains, tender lumps/bumps, sun sensitivity, scalp tenderness, color changes in hands/feet with cold exposure, persistent fever, and night sweats.

The tables below summarize the cumulative incidence through 3 years of any individual sign/symptom and the two most commonly reported individual sign/symptoms for each indication. Joint pain was one of the top two most commonly reported CTD sign/symptoms for all three surgical indications.

Augmentation	Number with sign/symptom reported	Cumulative incidence
Any Sign/Symptom	53	10.3%
Numbness of Hands	13	2.7%
Joint Pain	13	2.6%

Reconstruction	Number with sign/symptom reported	Cumulative incidence
Any Sign/Symptom	44	21.5%
Joint Pain	17	8.0%
Joint Swelling	10	4.5%

Revision	Number with sign/symptom reported	Cumulative incidence
Any Sign/Symptom	39	21.3%
Joint Pain	14	7.3%
Fatigue	11	6.0%

With respect to the comparison with the saline-filled BI data, Mentor compared the proportion of patients reporting a CTD S/S between the two populations. For the augmentation and reconstruction indications, the proportion of patients reporting a CTD S/S category was consistently higher in the SPS (saline-filled) versus the Core (gel-filled) study. There was no SPS data collected for revision patients, so comparisons to this group were not performed.

There were no statistically significant findings with respect to CTD S/S reporting in recipients of Mentor gel-filled implants and silent rupture, any rupture, patient dissatisfaction, and complications reported. However, the numbers of rupture patients were small; therefore, the lack of statistical significance could be due to lack of sufficient statistical power to detect a difference rather than lack of an association.

With respect to a comparison to the published literature, Mentor compared the Core Study data set of combined augmentation, reconstruction, and revision patients to primarily the Swedish study reported by Fryzek, et al. in 2001.[27] The proportion of patients reporting symptoms in the Core Study is consistently lower than that reported by Fryzek. However, a different questionnaire was used in the Fryzek reference, making comparisons difficult

With respect to the GEE (longitudinal) analysis in which patient age is used as a covariate, Mentor combined the augmentation, reconstruction, and revision data. Mentor was asked to provide this information for each indication separately. For **augmentation** patients, the following CTD signs/symptom increases from baseline were statistically significant and, therefore, were due to reasons other than aging: fatigue, exhaustion, joint swelling, frequent muscle cramps, joint pain, combined fatigue, combined pain, and combined fibromyalgia. Generalized aching was nearly statistically significant at p=0.0641. For **reconstruction** patients, the GEE analysis yielded no statistically significant results. Therefore, for the reconstruction population, it can be concluded that the increases noted in CTD signs/symptoms from baseline were due to aging. The symptom of joint pain, however, was nearly significant at p=0.0579 for reconstruction patients. For **revision** patients, the GEE analysis results indicated statistically significant findings for fatigue, generalized aching, and combined fatigue. Therefore, for this population, the increases from baseline in fatigue and aching were due to reasons other than aging.

Without a comparison group of women seeking plastic surgery similar in age, race, and socioeconomic status, but without implants, the clinical interpretation of these data is difficult. It is important to note, however, that joint pain is the one of the top two symptoms reported separately for augmentation, reconstruction, and revision patients. GEE analysis showed that changes from baseline in fatigue and/or joint pain were due to reasons other than aging for augmentation and revision patients. This was not observed in reconstruction patients.

Mentor also provided the proportion of patients reporting CTD S/S both before and after implantation, pooled across the 3 indications. The symptom types with the highest number of

patients with new reports in descending order are as follows: joint pain (39 new patient reports), fatigue (26 reports), numbness of hands (21 reports), back pain/stiffness (21 reports), frequent muscle cramps (17 reports), and neck pain/stiffness (16 reports).

In summary, the CTD S/S reports are consistently lower for the Core Study compared to the saline study. There appears to be no association between CTD S/S and rheumatologic disease diagnosis and rupture; however, the rupture rate is too low for statistical comparisons. Joint related symptoms and fatigue are reported with increased frequency for all three indications and do not appear to be related to aging for augmentation and revision patients. Without an appropriate comparison group, it cannot be concluded that these symptoms are specifically due to the implants.

11. Other Safety Data

In terms of additional safety data collected on the case report forms, reproductive and lactation problems were collected both preoperatively and postoperatively for all indications. Breast disease history was collected preoperatively for reconstruction and revision patients, and any new cases of breast disease were captured postoperatively for all three indications. Because interference of mammography by breast implants is a potential risk, Mentor also collected information on the number of patients who had postoperative mammograms, reports of abnormal masses, and follow-up findings. This information is summarized below.

Reproductive Problems – Before breast implantation, 214 (21%) of the 1,007 patients reported reproductive problems. Mentor did not collect details on the type of preoperative reproductive complications. Through 3 years after breast implantation, 10 patients reported the following reproductive problems: ectopic pregnancy (1 report) and miscarriage (9 reports). Mentor did not collect data in the Core Study on the number of patients attempting reproduction, but, instead referred to the general population-published miscarriage rate of 15.7%.[28]

Lactation Problems – Before breast implantation, 496 patients reported that they attempted to breastfeed, 492 reported no breastfeeding experience, and 19 did not respond to the question. Of the 496 patients who attempted to breastfeed preoperatively, 467 reported they had adequate milk, 94 reported inadequate milk, and the remainder did not respond to the question.

Postoperatively, 33 patients reported that they attempted to breastfeed. Of these 33 patients, 30 (91%) reported they had adequate milk and 2 (6%) patients (1 augmentation and 1 revision) reported lactation difficulties (one implanted via periareolar incision and other via an inframammary incision).

Breast Disease – For augmentation, patients were excluded from the study if they had active cancer of any kind. Through 3 years, there were no new cases of breast cancer reported.

For reconstruction, 169 patients had a preoperative history of breast cancer. Of these patients, 100 had been treated with chemotherapy, 35 had been treated with radiation, and 70 had been treated with hormonal therapy. Through 3 years, there were no new cases of breast cancer reported.

For revision, 39 patients had a preoperative history of breast cancer. Through 3 years, there was 1 new case of breast cancer reported - malignant breast disease. Patient [redacted] indicated no active cancer at time of study entry. The patient had no risk factors: she never smoked, had no current alcohol use, and no family history of cancer. The patient was never pregnant, began menarche at 13 years, and has not gone through menopause. In 1984, the patient underwent bilateral augmentation mammoplasty to correct for asymmetry. The patient was 46 years old at time of diagnosis, which was made 275 days after implantation with the study device (year 1 visit). The 1-year mammogram indicated a suspicious abnormality for both breasts (i.e., biopsy should be considered). The malignancy was considered severe; the tissue type was not specified. The diagnosis resulted in a lumpectomy with no breast implant removal.

Mammography – Mammograms were not required as part of the study. In addition, the average age of the study patients was below the age at which mammograms are typically recommended. Overall, 25% of the patients underwent postoperative mammograms. Through 3 years, 11 (4.1%) patients had a mammographic report of an abnormal mass (6 augmentation, 1 reconstruction, and 4 revision) without such a report at baseline. Of these 11 abnormal mammogram results, additional follow-up indicated only the 1 reconstruction patient described above had breast disease.

12. Effectiveness Data from Core Study

Effectiveness data from the Core Study consists of the following:

- Circumferential chest size and bra cup size in the augmentation patients or Restoration of chest mound in reconstruction and revision patients
- Global patient satisfaction (i.e., "Would you have the surgery over again?")
- Quality of Life (QoL) assessments.

Chest Size – As expected, all indications showed a significant increase from baseline with the implantation of the breast implant through 3 years.

Global Patient Satisfaction - Satisfaction data were collection on 97% of augmentation, 98% of reconstruction, and 96% of revision patients who were evaluated through 3 years. Satisfaction was based on a simple question of **"Would you have this breast surgery again?"** The table below summarizes the percentage of Yes responses for patient satisfaction at 2 and 3 years.

Global Patient Satisfaction		
Patient Group	**YES responses at 2 years**	**YES responses at 3 years**
Augmentation	99% (489/495)	97% (383/394)
Reconstruction	97% (179/184)	98% (119/121)
Revision	95% (160/169)	96% (132/137)

The table below summarizes the reasons why patients responded "no" to the global satisfaction question (i.e., would not have surgery again) at 2 and 3 years.

Reason for "NO" Response to Global Patient Satisfaction	# of Patients	
	At 2 years	At 3 years
Capsular contracture	1	
Wants saline breast implants	1	
Breast numbness / loss of sensation	2	
Scarring	3	1
Unknown	1	4
Pain	1	1
"Didn't realize could not get all gel from last implant out"	1*	
Patient said "for reconstruction after cancer"	1	
Unhappy with shape and size	1	2
Cost	1	
Patient is unsure	1	1
Multiple complications	2	1
Several breast surgeries – unusual events – unhappy with shape	1	
Terminally ill	1	
Bad experience with surgeon	1	
Breast "too heavy"	1	
"Would do again with different type implant"		1
Multiple surgeries		1
Palpability		1
Patient has not been comfortable with it		2
"Unsure due to life situations"		1
"Don't like feeling of chest axilla and back"		1
"Multiple infections and wrong size by previous surgeon"		1

* Revision subject whose previous non-study silicone gel implants had been revised because they had ruptured.

QoL Assessments – The QoL assessments include the Tennessee Self-concept Scale (TSCS), Short Form-36 Health Survey Scale (SF-36), Body Esteem Scale, Rosenberg Self-Esteem Scale, and Manitoba Cancer Treatment & Research Foundation Functional Living Index: Cancer (FLIC) (cancer patients only). Below is a summary of the findings for each assessment scale **through 2 years.**

The **Tennessee Self-concept Scale** summarizes an individual's feeling of self-worth, the degree to which the self-image is realistic, and whether or not that self-image is a deviant one. There are 100 items rated on a 5-point scale ranging from completely false (1) to completely true (5). For the augmentation and reconstruction indications, there was no significant change in the overall mean value of the total score across follow-up visits. For revision patients, there was a statistically significant decrease of 6.6 in the overall mean value of the total score across follow-up visits, suggesting a worsening in self-concept as measured by this assessment.

The **SF-36** is a generic measure of 8 health concepts: physical functioning; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health. The 8 scales can then be collapsed into two summary scales with the first 4 scales comprising the Physical Component Summary (PCS) and the last 4 scales comprising the Mental Component Summary (MCS). Augmentation patients showed a statistically significant decrease in the PCS (1.0) and

MCS (1.1) in the overall mean value across follow-up visits. Reconstruction patients showed no significant change in the PCS or MCS in the overall mean value across follow-up visits. Revision patients showed a statistically significant decrease in the PCS (1.8) and MCS (2.5) in the overall mean value across follow-up visits. However, the study populations continued to score higher postoperatively for all 8 subcategories and the MCS and PCS, as compared to the U.S. female population.

The **Body Esteem Scale** measures female body esteem for a variety of body parts and functions. Assessments include sexual attractiveness, weight concern, and physical condition. There are 35 questions that are rated on a 5-point scale ranging from strong negative feelings (1) to strong positive feelings (5); thus, the overall score ranges from 35-175. Lower scores indicate more strongly negative feelings about a body part or function. For the augmentation and reconstruction indications, there was no significant change in the overall mean value across follow-up visits. Among revision patients, there was a statistically significant decrease (worsening) of 5.0 in the overall mean value across follow-up visits.

The **Rosenberg Self-Esteem Scale** assesses global and uni-dimensional self-esteem, relating to an individual's overall feelings of self-worth or self-acceptance. There are 10 items rated on a 4-point scale ranging from strongly agrees (1) to strongly disagrees (4); thus, the overall score ranges from 10-40. A higher score indicates higher self-esteem. Among the augmentation patients, there was a statistically significant positive change of 0.6 in the overall mean value across follow-up visits. This indicates an increase in self-esteem based upon this instrument. There were no significant changes among the reconstruction and revision patients.

The **Functional Living Index: Cancer** is a subjective instrument designed to assess physical well-being, psychologic state, family situational interaction, social ability, and somatic sensation in cancer patients of the reconstruction and revision indication groups. There are 22 items rated on a 7-point scale. A statistically significant overall mean increase in the FLIC score was noted for delayed post-mastectomy patients (mean increase of 2.9), indicating improved functioning from pre- to postoperative. A statistically significant overall mean increase was also noted among revision patients who had a least one reconstruction revision or revision of an unknown indication, and a history of cancer (mean change of 5.0).

13. Effectiveness Data – QoL Literature Review

In addition to providing effectiveness data from the Core Study, Mentor provided a review of the quality of life (QoL) information available in literature. Mentor provided this review to support their contention that breast implants provide psychosocial benefits that are clinically meaningful for reconstruction and augmentation patients. Refer to Mentor's CD in Tab 4 of your Panel package for their review of the QoL literature.

Below is FDA's review of the relevant publications that Mentor provided. Mentor stated that they provided almost exclusively more recent publications because they believe that they are more reflective of current cultural norms on the issue of cosmetic and reconstructive surgery. They also focused on literature that evaluated clinical outcomes rather than motivations (i.e., preoperative mind sets). Thus, this is not an exhaustive compilation of the available publications on this issue for either augmentation or reconstruction patients.

Augmentation

A study of 47 women with subpectoral saline breast implants for primary augmentation uses a 69-item questionnaire, the Multidimensional Body-Self Relations Questionnaire (MBSRQ).[29] Three of the 10 subscales from the questionnaire are reported in this paper: appearance evaluation, appearance orientation, and body-area satisfaction. Appearance evaluation and body-area satisfaction reportedly measure similar factors. Appearance orientation measures the importance of appearance to the participant. The questionnaire was administered prior to surgery and at 3 and 6 months post-surgery. The methods section also describes a 4-part questionnaire to gain insight into patient's subjective thoughts on the outcomes of the surgery. The authors report that there was no difference pre- and post- op for appearance orientation, but patients scored significantly higher in their appearance evaluation and body-area satisfaction at 3 and 6 months after surgery. These outcomes are difficult to interpret for several reasons

- The response rate to the questionnaire was low at both 3 and 6 months (between 49-64% responded to the questions) and this could have introduced a significant bias. There is no comparison of respondents to non-respondents based on demographic or other factors.
- Although statistically significant, there is no explanation of the significance of the magnitude of change in the appearance evaluation or body-area satisfaction or the clinical relevance of this change.
- For both appearance evaluation and body-areas satisfaction, the change is diminished by 6 months.

Their postoperative questionnaire is difficult to interpret. Patients were asked how they felt the surgery affected their body image and whether they would have the surgery again. 96% of patients responded that their body image was affected positively, and 80% responded that they would have the surgery again. Only slightly over half (25/47, 53%) responded to this questionnaire.

One study examined patient psychosocial outcomes at 6, 12, and 24 months after surgery.[30] The study included 360 healthy women aged 19 and above from 24 U.S. clinical sites. There is no additional information on the inclusion criteria for this study. The surveys used were based on a survey described at the 1990 American Society of Plastic and Reconstructive Surgeons annual meeting and focus group questions. The 18 items on the post-surgical surveys were reduced to 3 psychosocial factors for analysis which were characterized as body-image improvement, self-image improvement, and sexual-social improvements. In addition, there was a question on "overall satisfaction with mammary augmentation surgery." The results reported that 91-94% of respondents reported "satisfaction with mammary augmentation surgery" at the three time points. At each postoperative period, 91-92% reported body image improvements and 88-86% reported self-image improvements. Between 43% and 51% reported sexual/social improvements. These results are difficult to interpret because the survey used was based on a modification of a survey that was not validated and the results reported were based on reducing the response to 18 items with scaled responses (from 1=not at all satisfied to 5=very satisfied) to 3 psychosocial factors. The item regarding "overall satisfaction with mammary augmentation surgery" is ambiguous and may have been misconstrued as referring to the surgery or the surgeon and not to satisfaction with breast implants. Women with capsular contracture within the first 6 months were more

likely to report lower overall satisfaction with surgery. Given this, exclusion of women who had bilateral explantation may have biased the results toward greater satisfaction.

A study of psychological effects of implant operations by Beale, et al.[31] was based on open interviews with a psychiatrist for 14 women before surgery followed by development of a structured interview based on the responses to these open interviews. The structured interview was subsequently applied to an additional 25 women pre- and 1 year post- surgery and to another 29 women 4 to 7 years after their implant surgery. In addition, the structured interview was also administered to a control group of 28 women visiting the otorhinolaryngology department who were there for non-cosmetic problems. The results from this study are difficult to interpret because only 25 women had the same pre-and post- implant interview. The study reports that, despite many complications, 78% of patients were "completely satisfied" with the outcome of the operation 1 year after surgery. This contrasts with 36% in the other study group who had implants from 4-7 years.

Sarwer, et al. (2003)[32] reported from their study of 30 women seen for an augmentation surgery consultation and 30 control women from the community, that women considering breast augmentation differed from controls by being more likely to report a life change in the past year and treatment by a mental health provider in the past year. Women seeking augmentation also scored higher on an appearance orientation subscale of the MBSRQ indicating their greater concern with their appearance. However women from the two groups did not differ on surveys evaluating their overall body image dissatisfaction but they did differ on a survey measuring body image dysphoria with breast augmentation patients reporting more frequent negative feelings about their appearance in social situations. This study did not have a follow-up after augmentation so does not bear on the issue of satisfaction with breast implants. Another study by Sarwer, et al. (2002)[33] described a survey of cosmetic surgery patients before and 6 months after surgery. Their hypothesis was that cosmetic surgery is body image surgery and that surgery would improve body image and diminish negative thoughts about body. Cosmetic surgery patients reported improvement in their satisfaction with specific body features altered by surgery and less dissatisfaction with their overall appearance. Of the 45 (out of 100) women in the study who completed both pre- and post-operative surveys, 6 were for breast augmentation, making generalizing the results to women with breast augmentation difficult.

Kilmann, et al. sent a 7-page questionnaire to 250 patients between 3 months and 32 months after augmentation mammoplasty.[34] 75 women responded to their survey on their expectations about the surgery prior to the surgery, their body and self image, and relationship with their partner. 57 of these women were in the same relationship with their partners before and after the surgery (consistent relationships). They reported that women in consistent relationships expectation for impact of surgery on their relationships was much greater than their actual impact but that these women perceived themselves as being more attractive and had a more positive body and self image after surgery than they expected before surgery. The results of this survey are difficult to interpret because women were asked to recall their state of mind before surgery compared to after surgery, in some cases nearly three years later. The large non-response to this survey could create a bias if the non-responders differed significantly from the responders.

Schlebusch and Mahrt[35] posed the question of whether patients benefit psychologically from augmentation mammoplasty. 30 women were evaluated pre-operatively, and 20 of them were subsequently reassessed 3 or more years later. There is no explanation of the reason the other ten were not assessed. The materials and methods stated that they were selected for the significant psychological distress preoperatively that had been a prime motivation for their surgery. It is not clear whether this applies to the 30 or the 20 women. 16 (80%) of these women complained about the lack of adequate information on the surgical procedure and the post-surgical complications, especially pain. The majority of these patients reportedly expected psychological changes as a result of implantation and 70% expressed improvements in self-confidence after surgery. 17 patients (85%) said they would have the surgery again. Before augmentation mammaplasty, 9 (45%) patients felt physically attractive as women but after surgery 14 (70%) did. 7 patients (35%) said their sense of self-worth was good or very good preoperatively, and 12 (60%) reported good or very good self-worth after surgery. Pre-operatively, 19 (95%) of these patients fitted the criteria for depression on the Beck Depression Inventory and 6 (30%) fit criteria post-surgically. Because of the patient selection criteria, the results should not be generalized to women after augmentation. While there were improvements in some parameters measured, others did not change.

A study by Young, et al.[36] described the degree of breast enlargement, as well as satisfaction and psychological impact of mammoplasty. Women were randomly selected from 355 women who had undergone mammoplasty with 10 surgeons at Barnes Hospital between 1980 and 1992. 120 women were contacted by phone, and 112 consented to be interviewed. Of these 112, 86% reported being completely or mostly satisfied with the operation. 81% would have the surgery again. 88% felt the implants made them more self-confident and 86% reported decreased self-consciousness. This study was performed without a baseline comparison for psychological characteristics with an untested survey which had not been validated. The results are, therefore, difficult to assess. Another publication by Young, et al.[37] detailed the results of an internet survey that was on-line from August 2001 through February 2002. The survey included 177 questions that were posted on a website, which also provided links to find a plastic surgeon for augmentation and includes photographs of successful breast implantations. The survey was completed by 2273 women who already had breast implants and 1738 who were considering augmentation. The results indicated a high level of satisfaction - 88% satisfied with results, 93% said they would recommend the procedure to friends or family, and 92% said the surgery improved their overall appearance. The self-selected population of respondents who visit a website about breast augmentation is likely biased. The experience of these women is unlikely to be representative.

In summary, the literature does not provide strong scientific support that breast implants have measurable psychological and psychosocial benefits for women seeking breast augmentation. The studies cited above are representative of the publications submitted by Mentor on this subject. Each study had one or more of the following problems that constrain interpreting results: short duration of follow-up (typically 3 months to 3 years); lack of an appropriate control population or baseline survey; use of different surveys before and after surgery; small study size; low response rate and/or high loss to follow-up; apparent exclusion of participants with adverse outcomes; limited to a single practice; use of instruments that have not been tested or validated; lack of clear description of inclusion and exclusion criteria; and outcomes of unknown clinical meaning.

Reconstruction

Assessment of psychological or psychosocial benefits from reconstruction is more complicated than assessing satisfaction or psychosocial benefits from augmentation. In addition to all the possible limitations described above for assessing augmentation patients, there are additional concerns for assessing cancer patients. A baseline measurement of psychological state prior to reconstruction (including implantation) is confounded by the impact of breast cancer diagnosis, decisions about treatment choices, reconstruction choices, facing a major illness, and uncertainty about the future. Improvements in psychological outlook post-reconstruction may be due to a myriad of factors such as relief over surviving a potentially fatal disease.

Other considerations may be that women who decide against reconstruction may differ psychologically to begin with (or may have a poorer or different prognosis), which may influence their decisions about reconstruction as well as their outlook after mastectomy. For instance, women who select reconstruction may base their feelings of satisfaction with outcomes on appearance, whereas women who do not choose reconstruction may base their satisfaction on the removal of cancer. These factors, and others, make a straight forward assessment of psychosocial or psychological assessment of breast implants for reconstruction difficult. A review on this subject is presented by Harcourt and Rumsey.[38]

The publications provided by Mentor on this subject are not an exhaustive review of the literature. It is also notable that papers that do not report at least some or a preponderance of improvements in quality of life or satisfaction are missing. As an example, Nissen, et al.[39] reported that "*Aspects of QOL other than body image are not better in women who undergo BCS* [breast conserving surgery] *or mastectomy with reconstruction than in women who have mastectomy alone. In fact, mastectomy with reconstruction is associated with greater mood disturbance and poorer well-being*."

Most of the publications provided by Mentor evaluated the prevalence of and reasons or psychological factors that influenced patient's selection of reconstruction or timing of reconstruction rather than outcomes after reconstruction. These papers are not summarized by FDA. Only studies that have a "mastectomy only" comparison group were reviewed because studies that have no appropriate comparison group are not informative on the issue of psychological or psychosocial benefit of reconstruction. None of the studies cited by Mentor compare reconstruction with breast implants specifically to other reconstructive procedures and to mastectomy alone.

Girotto, et al.[40] presented data from 316 consecutive women with breast cancer undergoing mastectomy with reconstruction between July 1997 and July 2001. The study purpose was to examine the effect of reconstruction on women 65 and older after breast cancer. Women were categorized based on age (65+ and <65 years). 24 women (8%) were at least 65 years and the remaining 92% were younger than 65. 12 of the 24 women (50%) age 65+ had breast implants for reconstruction. The other 50% underwent various autologous tissue procedures. Surgical choices and outcomes for women older and younger than 65 years are compared. The Medical Outcomes Study 36 Item short Form Health Survey (SF-36) was administered to these patients, but it is not clear from the protocol when, with respect to the timing of surgery, the survey was administered. The responses from women age 65+ were compared to age specific SF-36 population norms; SF-36 from study patients younger than 65 (but seemingly from another

study, not this one); and mastectomy patients age 55+ years from another study. The report stated that "*Older patients with breast reconstruction scored higher than age matched general population patients and previously reported mastectomy-only patients*." However, there is no statistical comparison of the responses of any of these groups, possibly because of the small sample size. Because of this, despite the appearance of higher scores based on viewing graphs provided, these results are difficult to assess. Others have opined that body image may be a more critical component for quality of life for younger than older cancer patients[41] and the seeming higher than normative scores could also be influenced by the relief from having survived a major illness and surgery. This could explain higher scores among older women with reconstruction. There was a comparison of the SF-36 scores from the 12 women 65+ with implants compared to the 12 women undergoing autologous tissue procedures. Patients with implants (12 of the 65+ patients of 24 undergoing reconstruction) scored lower in categories designed to test physical pain and role limitations but similar in areas measuring emotional limitations, vitality, mental health, etc. compared to other reconstruction patients. Again, because of the small sample size and lack of statistical analysis, the meaning of these findings is difficult to interpret.

Harcourt, et al.[42] examined the effect of mastectomy or immediate or delayed breast reconstruction on psychological distress, body image, and quality of life. They also assessed satisfaction with decisions post reconstruction. Any woman at 3 participating hospitals admitted for mastectomy or reconstruction were eligible for the study if they could communicate in English and were not cognitively impaired. In addition to a structured interview, women completed 3 standardized questionnaires: the Hospital Anxiety and Depression Scale; The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) including the breast cancer specific module which includes subscales on body image and sexual functioning; and a standardized Body Image Scale previously developed specifically for use with cancer patients. The final study group consisted of 103 patients: 56 mastectomy alone, 37 immediate reconstruction, and 10 delayed reconstruction. Result indicated that, before the operation, 32% of patients had high levels of anxiety (not statistically significant between groups). At the 6-month follow-up, the overall incidence of anxiety was reduced to 31% with the highest rate among women who had undergone immediate reconstruction (not significant). At 12 months, the anxiety incidence had increased to 39% with an increase incidence among the mastectomy and immediate reconstruction. An increased proportion of case levels of depression was also evident among mastectomy and immediate reconstruction groups but he overall incidence was still low. Changes in body images scores indicated that 39 women reported poorer body image scores at 1 year than they did before the operation. This was 36%, 49%, and 10% for the mastectomy, immediate reconstruction, and delayed reconstruction groups respectively. In this case, the timing of reconstruction seemed more important than reconstruction. A visual analog scale was used to measure satisfaction with the outcome of the surgical procedure. There were no significant differences among the 3 surgical groups at either of the follow-up points. The mean ratings between 6 and 12 months became slightly less favorable for women in the mastectomy or immediate reconstruction group but were slightly increased for delayed reconstruction patients. These data indicated that the psychological impact of reconstruction with breast implants or other methods is difficult to measure because of the mixed results depending on the issue as well as the timing of both the surgery (immediate vs delayed) and the timing of the follow-up.

In summary, assessing psychological or quality of life after breast cancer reconstruction with implants is complicated by numerous factors related to cancer diagnosis and the stress of rapidly making decisions on treatment and reconstruction options. There may be differences between satisfaction with specific reconstructive procedures (e.g., breast reconstruction with implants versus autologous tissue transfer, or combinations of implant and autologous tissue transfer). Literature that adequately evaluates the short-term or long-term psychological or psychosocial benefits of breast implants as a reconstructive procedure utilizing appropriate control group was not provided by Mentor.

14. Statistics for Core Study

In terms of the validity of the data analysis, presentation, and conclusions, no major statistical deficiencies were identified. Mentor provided numerous confidence intervals to judge the precision of the complication rates. Bias in reported incidence rates appears to be minimal because loss to follow-up was minimal. Because women remained in the study after experiencing an adverse event (with the exception of explant), they were available to experience another adverse event. Thus, the study did not have the problem of competing risks.

Mentor performed an extensive covariable analysis as it related to the adverse events of most interest. The covariables examined were age, race, smoking, surgical approach, surgical placement, incision size, surface type, prior tissue expander, irrigation solutions used in the pocket, implant size, and site. Their effect on the following complications was examined via Cox regression analysis: infection, rupture, capsular contracture, high/low nipple sensitivity, high/low breast sensitivity, explantation, and reoperation. One noteworthy finding was that the Cox regression analysis did not determine surface type to be a significant covariable related to capsular contracture III/IV. Therefore, any claim about reduced rate of capsular contracture with the textured implant would be unsubstantiated.

Mentor provided a table for the major categories of rheumatological signs and symptoms which reports the frequencies at baseline, 2 years, and 3 years, along with a GEE model test of each complication/symptom adjusted for age (of patient). It is important to note that the 3-year data were based on 665 of the 1007 original patients, excluding 266 patients who were not yet due for their 3-year follow-up. (Other excluded were deaths, explants, and lost to follow-up.)

Statistical issues related to rupture are discussed in Section J below.

Effectiveness was demonstrated by increase in breast size, patient satisfaction, and QoL assessments. Ninety-eight percent of patients would have the surgery again, including 95% of those who underwent a reoperation.

Mentor's data collection, analysis, and presentation are all acceptable from a statistical standpoint. The adequacy of 3-year follow-up (especially for rupture) and the acceptability of the observed complication rates must be evaluated from a clinical perspective.

J. RUPTURE RATE AND HEALTH CONSEQUENCES

Implants can be suspected of rupture because of symptoms such as flattening of the implant or pain (suspected symptomatic rupture) or because of definite or indeterminate findings of rupture on MRI (suspected silent rupture). FDA believes that confirmation of rupture status occurs at explantation (implant removal). At explant, suspected implant ruptures are identified as either confirmed intact or confirmed ruptured. Some implants are removed for reasons other than suspected rupture (e.g., to correct a cosmetic complication, to treat capsular contracture, to change implant size), and the implants may be found to be ruptured at the time of explant.

When a silicone gel-filled breast implant ruptures, the patient and the physician may be unaware of it, the body does not have a mechanism for eliminating the silicone gel, and the gel can migrate outside of the capsule into the breast area, the lymph nodes, and distant locations. Accordingly, FDA recommends that a sponsor provide data with follow-up of sufficient duration to adequately describe the rate and rate of change of local complications over time (with specific concern with rupture), to describe the frequency of ruptures observed (intracapsular, extracapsular, and migrated gel), and to characterize the potential local health consequences of their ruptured implants. The study duration should be, for example, sufficient to measure or reasonably estimate how the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device. These data may come from the Core Study or other sources, such as the Adjunct Study and literature. These concerns were conveyed by FDA in Mentor's 4/14/04 major deficiency letter. Below is a summary of the information provided by Mentor to address these issues, stratified by data source, followed by FDA's conclusions.

1. Mentor Core Study

Recall that a subgroup of the Core Study were to have MRI screening for rupture at years 1, 2, 4, 6, 8, and 10 after implantation. 420 women (with 785 implants) agreed to participate in the MRI screening study. Of these 420 women, 17 patients never had their first MRI, leaving 403 possible patients. At the 1 year MRI visit, MRIs were obtained in 326 women (78% of 420 patients), and at the 2 year MRI visit, scans were obtained in 372 patients (89% of 420 patients).

Table 1 below summarizes the patient accounting for the MRI Cohort at the 1 and 2 year MRI timepoints. Recall that the MRI substudy was designed to enroll 405 patients to achieve 324 patients at 2 years to estimate a rupture rate of 5% at 10 years with adequate precision.

Table 1: By-implant accounting for MRI Cohort in MRI study at the 1st and 2nd MRI timepoints.

	Augmentation N = 202 patients N = 417 implants	**Reconstruction N = 134 patients N = 211 implants**	**Revision N = 84 patients N = 157 implants**
1st MRI at 1 year			
Theoretically Due	417	211	157
Deaths	0	0	0
Device Removals	1	10	7
Expected	416	201	150
Actual	324	164	125
% Follow-up	77.9%	81.6%	83.3%

	Augmentation N = 202 patients N = 417 implants	**Reconstruction N = 134 patients N = 211 implants**	**Revision N = 84 patients N = 157 implants**
2nd MRI at 2 years			
Theoretical	417	211	157
Deaths	0	2	0
Device Removals	4	11	10
Expected	413	198	147
Actual	374	185	136
% Follow-up	90.6%	93.4%	92.5%
Mean duration of implantation at 2nd MRI	2.2 years	2.1 years	2.1 years

When rupture is defined as a possible or indeterminate rupture noted on MRI by either the Local or Central radiologist without confirmatory explantation or repeat MRI, review of the data provided by Mentor indicates that there were a total of 8 ruptured implants in 6 patients in the MRI cohort: 1 implant in 1 augmentation patient (#[redacted] at 25 months, 1 implant in 1 reconstruction patient (#[redacted]) at 23 months, and 6 implants in 4 revision patients (#[redacted] #[redacted], #[redacted], and #[redacted]), at 23 months, 24 months, 28 months. Although Mentor's final determination of rupoture status for patients[redacted] and [redacted]states no rupture, these patients were included in the rupture rate because there have been no confirmatory explantation performed for these patients.

Table 2 below shows the KM rupture rate for the MRI Cohort, for these 8 implant ruptures in 6 patients.

In the event that the explanted device is sent to Mentor's laboratory, it is the explanting surgeon's visual assessment at the time of explantation which has determined the final rupture status – either intact or ruptured – for the purposes of the Core Study. As previously discussed in Section D (**Modes and Causes of Rupture**), there were 4 implants in which the laboratory results indicated surgical instrument damage, but the explanting physician identified the implants as intact and are, therefoore, not included in this rupture rate: [redacted] (1 implant); [redacted] (2 implants); and [redacted] (1 implant).

Additionally, there was one implant in a reconstruction patient (#[redacted] which indicated rupture at the 1-year MRI, but showed no evidence of rupture by either the local or central radiologist at the 2-year MRI, which Mentor claims is intact and is not included in this table. FDA believes that until confirmatory explantation is performed, this implant should be included in the rupture rate as a worst case.

As previously discussed, there were no symptomatic ruptures reported in this study, and there were no silent ruptures noted incidentally upon explantation in the non-MRI group.

Mentor used the information available to calculate a total rupture rate over time for the patients enrolled in the Core Study. The 3-year rate is based on only partial data as ≈26% of the patients had not yet achieved 3 years of follow-up.

Table 2: By-patient and by-implant cumulative KM risk rate of rupture through 3 years[1] for MRI Cohort of Mentor Core Study.

	By-Patient		By-Implant	
	Rate	**95% CI**	**Rate**	**95% CI**
Augmentation	0.5%	(0.0, 1.5)	0.2%	(0.0, 0.7)
Reconstruction	0.8%	(0.0, 2.2)	0.5%	(0.0, 1.4)
Revision	4.8%	(0.2, 9.3)	3.9%	(0.8, 6.8)
Overall	1.4%	(0.3, 2.6)	1.0%	(0.3, 1.7)

[1]Only partial data is available at 3 years. MRI assessments were performed at years 1 and 2. All ruptures reported in the Core Study were silent ruptures and were found only in the MRI Cohort. The MRI Cohort is only approximately one-third of the total Core Study population.

Below are the histories for patients in the MRI Cohort with MRI-suspected rupture from the Core Study that were provided by Mentor.

Of the patient in the MRI substudy of the Core Study, Mentor reports one **revision patient (-[redacted]** with bilateral implants confirmed to have bilateral implant ruptures at explantation. This patient originally had bilateral implants placed in 1984 at the age of 31 years for augmentation. She enrolled in the Mentor Core study in November of 2000 as a revision patient due to rupture and severe capsular contracture of the right implant, and she had bilateral textured round implants placed in the subglandular position with a capsulectomy on the right. Approximately nine months after her revision surgery (8/01) and entry into the Mentor Core Study, the patient suffered an embolic stroke presenting as right hemiparesis and dysarthria. A TEE and genetic studies for hypercoagulability disorder were reportedly negative. She reportedly developed a venous thrombus in her left forearm at a prior IV site, and was started on coumadin. Two months later, she presented with a pulseless, blue left hand, with an unsuccessful attempt to revascularize. She also was noted to have a perinephric hematoma, necessitating discontinuation of coumadin, and initiation of vitamin K therapy and blood transfusion. She ultimately underwent amputation of her left hand (10/01) and remained on coumadin therapy.

She had her first screening MRI for implant rupture as a member of the MRI cohort on 3/02, and no evidence of rupture was noted by both the local and central MRI radiologist. At her second scheduled screening on 2/03, the local reader noted bilateral keyhole signs indicative of rupture. The central reader read the films as indeterminate for rupture and suggested repeat scans. She had her third MRI on 12/03, and the local reader noted prominent keyhole deformities, confluent folds, bubbles within the silicone signal in both implants consistent with implant rupture, as well as silicone signal intensity extrinsic to the capsule on the right implant which was believed to represent extracapsular silicone. The patient's ruptured implants were eventually removed on 3/04, one year after her initial MRI indicated clear signs of rupture. The surgical note at this time does not specifically state whether or not extracapsular silicone was present. The presence of implant rupture was described in the note, as well as the removal of both capsules. Her implants were replaced with another set of Mentor implants, placed subglandularly via the inframammary approach with a 6cm incision. The ruptured implants were sent back to Mentor for evaluation, and a large tear measuring 21cm was noted in one implant and an area measuring 7cm x 6cm was missing from the other implant. Microscopic evaluation revealed no indication as to the cause of the tear in the one and hole in the other implant. At her last visit, the patient

was complaining of a 1cm lump in her right breast area at 8 o'clock of the areolar border. Her current medications are synthroid, aspirin, coumadin, trazodone, paxil, and pravachol.

There was another MRI Cohort patient who underwent exploratory surgery due to MRI-suspected ruptures: **patient [redacted] (revision)**. This patient's left implant was removed, visually inspected and noted to be intact, and then re-implanted. To explore the right implant, the incision was opened down to the implant, the implant was not removed or inspected, and the implant was noted to be intact. Mentor categorized these implants as intact.

Patient [redacted] was originally implanted with McGhan silicone gel-filled implants in 1985 at the age of 29. She noticed a change in the shape of the R implant and underwent her first revision surgery 10 years later in 1995 with bilateral Mentor saline-filled implants placed in the submuscular position. At the time of this first revision in 1995, the right implant was ruptured with free silicone noted contained within the capsule. She entered the Mentor Core Study on 6/01 at the age of 45 when her L saline-filled implant deflated one month earlier, and she received bilateral textured Mentor gel-filled implants in a submuscular position; this was her second revision (third set of implants). She had R breast trauma in an automobile accident about 8 months after entering the Mentor Core study. Her first MRI on 4/17/03 was read by the local radiologist as having no signs of intracapsular rupture but evidence of free silicone in both breasts and bilateral radial folds, suggestive of extracapsular rupture. She had an ultrasound (U/S) examination one year later on 5/12/04 which reported enfoldings of both implants, sonographically intact implants, and there was no mention of free or extracapsular silicone. The U/S report acknowledged that MRI is a more sensitive method of detecting implant rupture. The central radiologist recommends a repeat MRI. Mentor believes that the extracapsular gel is due to the previous rupture. FDA believes that until confirmatory explantation is performed, these implants should be included in the rupture rate as a worst case. Therefore, Mentor included both implants in the rupture rate.

Patient [redacted] was originally implanted with augmentation silicone gel-filled implants in 1978 at the age of 29. In 1983, 5 years later, her L implant was replaced due to rupture. Both implants were replaced in 1984; the R implant was ruptured and the patient was dissatisfied with the shape of the L implant. She entered the Mentor Core study as a revision augmentation patient on 11/10/00 due to bilateral capsular contracture and malposition of the R implant. This was her 4th L implant and 3rd R implant. The surgical op note at the time of enrollment in 11/00 indicates that the removed implants were not ruptured. She missed her Year 1 MRI. The Year 2 MRI was read by the local radiologist as showing an intact R implant. The L implant MRI was read by the local radiologist as showing a small focus of intracapsular silicone adjacent to the shell in the upper outer aspect with no definite collapse or rupture of the shell of the L implant. The final reading was indeterminate for rupture of the L implant by the local reader. The central reader concurred with this reading. FDA believes that until confirmatory explantation is performed, this implant should be included in the rupture rate as a worst case. Therefore, Mentor included this implant in the rupture rate.

Patient [redacted] was originally implanted with augmentation silicone gel-filled breast implants in 1976 at the age of 27. She developed capsular contracture and had implants replaced in a subglandular position on 4/18/01 when she entered the Mentor Core Study. She complained of bilateral unacceptably low nipple sensitivity and month after her surgery, she developed a

hematoma on the L which was evacuated. In 1/02, she was reported to have Baker Grade III capsular contracture on the L, which was treated with closed capsulotomy. The patient missed her year 1 MRI. At the time of her year 2 MRI on 3/11/03, she was still noted to have capsular contracture on the L and was also complaining of unacceptably low breast sensitivity on the L. Her MRI was read as showing an early intracapsular rupture on the L by the local reader. The central reader also noted prominent folds. It was recommended that the patient undergo a repeat MRI scan. The patient has refused requests to have a repeat scan. The patient's surgeon does not believe that her implant is ruptured. FDA believes that until confirmatory explantation is performed, this implant should be included in the rupture rate as a worst case. Therefore, Mentor included this implant in the rupture rate.

Patient [redacted] underwent mastectomy with latissimus flap and a Mentor Spectrum tissue expander placement on 10/00 on the L following a diagnosis of breast cancer at the age of 33. One year later, she was implanted with a submuscular textured Mentor gel implant on the L and entered the Mentor Core study. At her year 1 MRI on 11/13/02, both the local and central radiologists noted no evidence of rupture. At her year 2 MRI on 8/29/03, the local radiologist noted hyperintense material, probably within a lymph node, which would indicate an extracapsular rupture; however, there was significant artifact noted on the films due to movement of the patient during the examination. Compared to the previous MRI, the area of increased intensity was present on the year 1 MRI but was noted to be very subtle at that time. The Central radiologist's reading indicates that the scan quality was "good," noting that there was no abnormal lymph node and trace peri-implant fluid. The surgeon did not agree that there was a rupture and that, because the patient was dying of cancer, he did not feel it was "appropriate or important to prove or disprove" his impression. The patient died of breast cancer in January 2004 before additional imaging studies could be conducted. Mentor included this implant in the rupture rate.

Patient [redacted] underwent breast augmentation on 4/27/01 with subglandular smooth implants at the age of 42. At her year 1 MRI on 5/28/02, the local radiologist read the MRI as suspicious for rupture on the R due to the presence of prominent folds. The central reader noted no evidence of rupture. At her year 2 MRI on 4/30/03, the local reader again noted a peculiar complex fold pattern involving the lower inner quadrant of the R implant, which was confluent from anterior to posterior, and with silicone appearing on both sides of the fold. The central reader noted prominent folds but no evidence of rupture on the R. Based on his physical examination, the surgeon believed that the rupture is actually a "buckle in the implant." He notes, "I have assured this patient that I don't feel any problem exist[s] and that I have reviewed the reports." This patient reported mild implant wrinkling in 6/04 and is scheduled to have her 4-year MRI in 2005. FDA believes that until confirmatory explantation is performed, this implant should be included in the rupture rate as a worst case. Therefore, Mentor included this implant in the rupture rate.

For reconstruction **patient** [redacted], Mentor claimed that the L implant was not ruptured on the basis of a follow-up MRI showing no rupture. The first MRI scan, performed 2½ years after implantation was read by the Local radiologist as two areas of probable extracapsular silicone around the left breast and in the left axilla, with no evidence of intracapsular rupture. The Central radiologist believed these to be artifact and read the scan as indeterminate for free silicone on the left. A subsequent MRI scan performed 1 year later showed absence of the high

signal areas with no shell discontinuity and no extraluminal silicone. Mentor did not include this implant in the rupture rate. However, FDA believes that until confirmatory explantation is performed, this implant should be included in the rupture rate as a worst case.

In summary, the Core Study provides rupture rate information in the MRI Cohort with complete 2-year and partial 3-year data. These data are of limited value to address the rupture rate over the lifetime of the device due to the short duration of follow-up. In addition, these data are of limited value to address the local health consequences of rupture due to the small number of ruptures observed.

2. Sharpe and Collis MRI Study

To address the long-term rupture rate of their devices, Mentor provided a summary of an unpublished case series of patients in Dr. David T. Sharpe's plastic surgery practice in the U.K. Of the 1,140 patients in his database, Dr. Sharpe identified 204 of his patients who underwent breast augmentation with subglandular Mentor textured silicone gel-filled breast implants at the U.K. National Health Service (NHS), who did not have any additional surgical procedures by him, who were asymptomatic, and who did not have capsular contracture or any clinical evidence of rupture. Therefore, this case series describes augmentation patients from one surgeon who were reportedly asymptomatic during the duration of their having breast implants, and who had their implants remaining at the time of MRI examination. These women were invited to undergo MRI scanning for silent rupture with a scanner which was appropriately strong enough to detect a rupture (i.e., 1.5 Tesla) and which contained a dedicated breast coil. Of these 204 women, 101 women (50%) agreed and had one MRI scan. These 101 women who underwent this one MRI scan had a total of 204 implants.

The mean implant duration for these patients was reported to be 8.8 ± 2.5 years. Mentor provided a breakdown of the number of women/implants at each time point, and the minimum duration of implantation appears to be 4.0-4.9 years. There were 19 implants in 12 patients which had evidence of MRI rupture. Of these 12 patients (19 implants) with suspected rupture via MRI, there were 11 patients (18 implants) who underwent explantation in order to confirm the rupture status. Of these 18 implants with suspected MRI rupture in which explanation was performed, 11 were confirmed to be ruptured at explant (61%). The mean duration of implantation for these 11 confirmed ruptured implants was reported to be 9.1 ± 1.6 years. There were no extracapsular ruptures observed in this case series. In summary, the by-implant point prevalence of silent implant rupture in this case series of asymptomatic augmentation patients in the U.K. from one investigator is 5.4% (11 of 204 implants) with a mean implant duration of 8.8 years (range 4-12 years).

The authors assert that the implant duration in this case series represents exclusively "third generation implants," which is why their data is not comparable to that observed by Brown, et al.[43] in 2000. The authors also assert that this study represents exclusively asymptomatic silent rupture, which is why their data are not comparable to those reported by Gabriel et al.[44] in 1997. The authors compared their rupture rate of 8.9% (mean implant duration = 8.8 years), to 6% rupture rate for "third generation" implants in Hölmich, et al. (2003) (median duration was 6 years for third generation implants).[45] This 6% rupture rate observed in the third generation implants represents 62% of the total implants studied by Hölmich, and represents implants mostly implanted in a submuscular rather than subglandular placement.

Mentor notes that the case series by Drs. Sharpe and Collis reports implants exclusively implanted in a subglandular position, never via a periareolar incision, and with exclusively textured implants used. For the data reported in the U.S. for Mentor Core Study augmentation patients, 70% of implants used were smooth rather than textured, 23% of implants were placed via a periareolar incision (most, 59%, were placed inframammary), and 67% of implants were placed in a submuscular or subpectoral position rather than a subglandular position.

According to the IOM report[46], the subglandular position may be associated with a higher capsular contracture rate than with the submuscular position. For the Core Augmentation cohort, Mentor also found that subglandular placement was associated with higher risk of capsular contracture Baker Grade III or IV, based on Cox Regression findings. Explant studies of sufficient size (i.e., over 300 implants) published after the IOM report, indicate a positive correlation between severe capsular contracture and implant rupture.[47] All of the patients in the Sharpe/Collis study had their implants placed in a subglandular position, which is associated with a higher capsular contracture rate, according to the IOM report. However, patients with capsular contracture were excluded from the Sharpe/Collis study. Given that severe capsular contracture is associated with implant rupture, the authors have excluded the patients at high risk of rupture from their MRI evaluation, underestimating the true silent rupture risk in their population. Therefore, by excluding patients with capsular contracture and including only patients with subglandular placement, Sharpe/Collis have studied patients with the lowest risk of implant rupture.

Additionally, there appear to be significant differences in implant position and in surgical approach between the U.K. Sharpe/Collis study and the U.S. Mentor Core Study. These differences in surgical practices between the two countries would be expected to significantly affect the implant rupture outcome. Because these differences in surgical practice may significantly affect rupture outcome, the utility of predicting rupture outcome for the U.S. population from these data is limited.

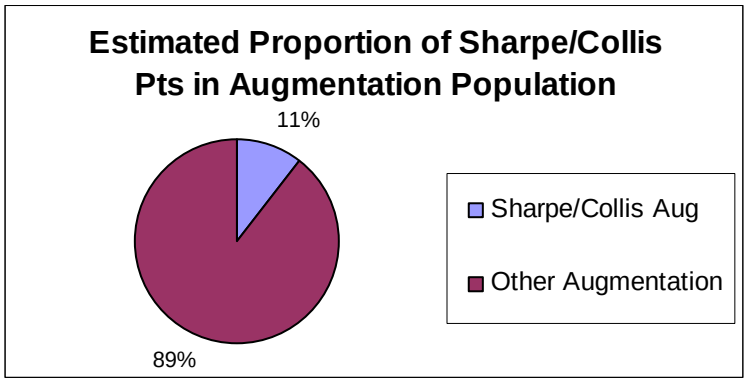
Finally, the authors performed a single MRI scan (and in only a subset of 50% of the patients who consented to MRI) rather than serial scans**.** This single scan results in a point prevalence rather than a rate over time. A point prevalence is the proportion of a defined population (cohort) at risk for a disease or event (e.g., rupture) that is actually affected by that event at a specified point in time. It can be thought of as a cross-sectional look or "snapshot" in time. Persons experiencing rupture before the time at which the snapshot is taken will not be included. Therefore, a point prevalence does not address the issues of the occurrence of new events in the population per unit time (incidence rate), or the cumulative risk (probability) of experiencing an event over a given time period (e.g., 10 years). The question of what proportion of implants is ruptured by 10 years (i.e., cumulative risk) would best be answered using survival analysis. To calculate either incidence rate of rupture or cumulative risk over a given time period, serial MRI scans are needed.

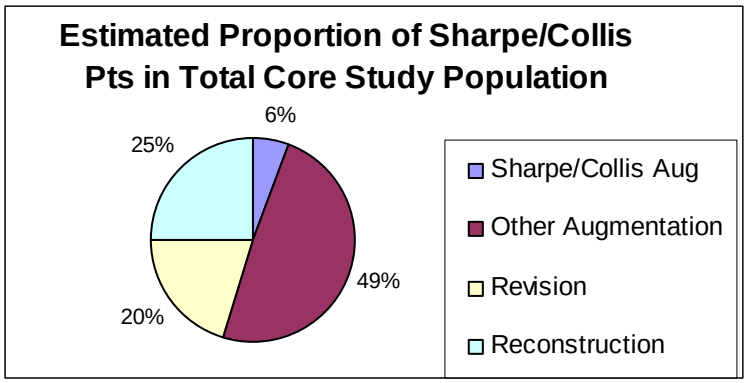
In summary, the issues below describe why the Sharpe/Collis data are of limited value in characterizing the rupture rate and the rupture rate over the lifetime of Mentor's breast implant device:

- The data relate only to augmentation patients, and generalizability to the reconstruction and revision indications is not possible.

- The data describe a case series from a single surgeon.
- The data describe MRI's performed based on voluntary participation on only a subset of the patients from one surgeon's practice, resulting in possible selection bias.
- The data exclude patients with capsular contracture, who are at higher risk of having rupture.
- The data exclude patients who had prior surgical procedures (i.e., such as biopsy), who are at higher risk of having rupture.
- The data exclude patients who had their implants removed prior to 4 years after implantation, underestimating the rupture rate.
- All implants in the data are textured and placed in a subglandular position. Whereas, the majority of implants in the Core Study augmentation population were smooth (not textured) and not placed subglandularly, indicating differences in surgical practices between the U.K. and U.S., which may affect rupture outcome.
- The data describe the point prevalence of rupture rather than rupture rate over time.

To illustrate the proportion of patients in the Mentor Core Study to which the Sharpe/Collis data apply, Mentor provided the number of augmentation patients who had no surgical procedures (including explant); no CC grade III, IV, or indeterminate/unspecified; no smooth devices; no periareolar incision surgical approach; and subglandular placement. There were 58 patients in the Core Study augmentation population who met all of these criteria. The figures below show the proportion of patients in the Core Study who met the Sharpe/Collis entry criteria for the augmentation patients only and for the entire Core Study population as a whole. Both figures show that patients meeting the Sharpe/Collis entry criteria apply to a minority of patients in the Mentor Core Study.





Mentor also referred to this Sharpe and Collis study to address the frequency of intracapsular vs. extracapsular gel and the potential local health consequences of implant rupture. However, there were no cases of extracapsular rupture reported in the Sharpe and Collis study. Recall that this study represents a case series of augmentation patients (which represent a subset of the total practice of the authors) who did not have complications or surgical interventions, who had exclusively subglandular placement (in contrast to predominantly submuscular placement in the Mentor Core Study), who still had their original implants, and who had one MRI evaluation rather than serial MRI evaluations. Of the 11 implants in 9 patients confirmed to be ruptured at explant (recall that only 18 of 19 implants identified as ruptured on MRI were explanted), some patients had a rheumatological examination (the authors did not report how many of the 9 patients with confirmed ruptured implants actually had a rheumatological evaluation). Of the patients with ruptured implants who had a rheumatological evaluation, one patient was found to have an episode of "myalgic encephalitis." The specific signs/symptoms/physical findings associated with the diagnosis was not provided. *The Sharpe/Collis data, therefore, provide limited information to characterize the frequency of intracapsular vs. extracapsular gel and the potential local health consequences of implant rupture.*

It should be noted that in a 2/28/05 email, Mentor provided new information regarding the Sharpe/Collis study population in addition to that provided in their August 2005 amendment to their PMA. In this email, Mentor stated that there were 14 women (the number of implants was not provided) who had revision surgery primarily due to capsular contracture and who were excluded from the original 204 eligible women for MRI. Although the study protocol states that patients with Baker III/IV capsular contracture would be excluded, Mentor stated that there were 9 patients with Baker III capsular contracture, 5 of whom were evaluated by MRI and included in the 101 women who agreed to undergo MRI. Mentor also stated that there were 2 patients with Baker IV capsular contracture who were evaluated by MRI. Although the study protocol states that patients with surgical interventions would be excluded, Mentor stated that there were also 3 patients with mastopexy procedures, of whom 2 were invited to participate in the study but declined. In addition to this email, in a telephone conversation on 3/1/05, Mentor stated that this information was recently obtained from the study authors via review of their patient records. Therefore, this information was retrospectively obtained. *This email does not include any raw data, summary data tables, or revised Sharpe and Collis study report. In addition, it is unclear why some patients who met the stated exclusion criteria were in fact included in the study. Accordingly, FDA did not revise the information summarized above for the Sharpe and Collis study based on this 2/28/05 email information.*

3. Danish Literature Data – Rupture Rate

Approximately 56% of the women in the Danish Registry for Plastic Surgery are implanted with Mentor gel-filled devices, according to Mentor. Mentor provided no additional information from the Danish Registry. However, below is a summary of several publications of Danish data regarding the incidence and prevalence of silent rupture rate.

Hölmich, et al. in 2001[48] reported on the prevalence of rupture via MRI of a subset of augmentation patients. Patients who had their surgery between 1973 and 1997 were randomly selected to undergo MRI in 1999 for rupture detection. There were 271 women with 533 implants reported, with 183 of these implants identified as "third generation" (i.e., implanted after 1988), 130 identified as "second generation" (i.e., implanted 1979-1987), 9 identified as "first generation" (i.e. implanted 1974-1978), and 211 with missing identity. The median duration of implantation was 12 years (range 3 to 25 years). The youngest implants are 3 years old. Therefore, the data are applicable only to implants which survive without removal for at least the first 3 years following implantation.

There were 141 of the 533 implants with definite rupture (26% of implants) observed in 97 of the 271 women (36% of women). Of the 141 ruptures, 110 implants (78%) were intracapsular and 31 (22%) were extracapsular. An additional 32 implants were determined to be possibly ruptured. If definite and possibly ruptured implants are considered, then 173 of 533 implants (32%) were ruptured. The prevalence of rupture was highest for second generation implants (N = 130 implants), lowest for first generation implants (N = 9), with third generation implant (N = 183) prevalence rates low.

The manufacturers included in this study were as follows: McGhan/3M (n = 146), Dow Corning (n =101), Surgitek/Bristol (n = 78), Nagor/Remploy (n = 43), Eurosilicone (n = 18), Misty/Bioplasty (n = 18), Heyer Schulte/Baxter (n = 13), CUI/Cox-Uphoff (n = 10), Kocken (n = 6), and unknown (n = 100). Some of these implants are only available in Europe. Note that one of the three MRI centers, which involved 203 of the 533 implants, utilized an MRI machine with a magnet which was not sufficiently strong enough to provide reliable scans. This may have biased the data, resulting in an underestimation of the rupture rate. The applicability of these data to predict the rupture rate and rate over time for the Mentor product is limited.

In a subsequent study, Hölmich, et al. (2003)[45] reported on the incidence of implant rupture based on the results of a second MRI performed in 2001 on the above women who still had their implants and who agreed to a second MRI. The one center described above which utilized an underpowered magnet was excluded for the second MRI. The patients therefore underwent serial MRI over a two year period, once in 1999 and once in 2001 at 2 centers.

The median duration of implantation was similar to that of the previous study: 12 years (range 3 to 25 years). There were 317 implants in 186 women included. Approximately two-thirds of the implants (N = 197) were "third generation" (i.e., implanted in 1988 or later); 91 implants were "second generation" (i.e., implanted 1979-1987), and 29 were "first generation" (i.e., implanted 1974-1978). The youngest implants are 3 years old; therefore, the data are only applicable to implants which were not removed within the first 3 years of implantation. Therefore, the data

are only applicable to implants which survive without removal for at least the first 3 years following implantation.

There were 33 total definite ruptures, 26 of which were diagnosed by MRI and 7 which were incidentally found at repeat surgery. Of the 26 MRI-diagnosed ruptures, 6 were extracapsular. There were 23 total possible ruptures, 22 of which were identified by MRI and 1 which was reported at surgery as "sticky" but intact. The total rupture incidence for definite rupture was 5.3 ruptures per 100 implants per year (95% confidence interval 3.5 – 7.1). For MRI-diagnosed ruptures, the rate of definite rupture is 4.4 per 100 implants/year (95% CI 2.7–6.1). The total rupture incidence rate for definite or possible ruptures was 8.9 ruptures per 100 implants per year (95% confidence interval 6.6 – 11.3). Because the authors state in the discussion section that they believe that the true rupture rate is closest to the combined group of definite and possible ruptures, it is 8.9 ruptures/100 implants/year that is the more realistic value to address the rupture rate because it includes both definite and possible ruptures.

For third generation implants which do not rupture in the first 3 years, the authors estimate a rupture rate of 2% at 5 years, and 15% at 10 years. This is based on 197 of the 317 implants which they categorized as "third generation" (i.e., implanted at year 1988 or later). They point out that a survivor bias may have influenced this estimate, yielding a rupture estimate which is too low, because the implants included had to remain intact for 3 years and because implants explanted before the first MRI were excluded. Another limitation which the authors fail to point out is that this projected estimate over time is based on the assumption of a linear shape for the rupture curve. With only two time points for MRI assessment, the shape of the rupture curve cannot be assumed to be linear. The authors describe a prior small pilot study in which the sensitivity of MRI was 86% with a specificity of 100%, and they acknowledge that because of the high specificity relative to sensitivity, some ruptures may have been missed.

In a more recent publication, Hölmich, et al.[49] in 2005 found a specificity of 97%, sensitivity of 89%, positive predictive value of 99%, and negative predictive value of 79% for MRI in detecting rupture. For the diagnostic ability of MRI to accurately detect rupture, these are excellent values; however, this does mean that MRI missed 11-14% of the implant ruptures in the Danish literature data.

4. Danish Literature Data – Health Consequences

Below is a summary of several publications of Danish data to characterize the incidence of intracapsular gel and extracapsular gel rupture, progression of intra to extracapsular rupture, and local breast symptoms associated with implant rupture for silicone gel-filled breast implants, in general. These literature references are not specific to Mentor devices.

Hölmich, et al.[48] in 2001 reported that of the 141 implant ruptures noted on MRI, 31 implants (22 %) were noted to be extracapsular. In 2003, Hölmich, et al.[45] reported that of 26 MRI-diagnosed ruptures, 6 (23%) were described as extracapsular. In both the 2001 prevalence and 2003 incidence studies, approximately one-fourth of the ruptures were noted to be extracapsular with three-fourths of the ruptures as intracapsular. Recall that the 2001 study reported on the prevalence of rupture in 271women who underwent a singe MRI screening of their cosmetic implants (median in-vivo age of implants 12 years, range 3 – 25 years) in 1999. The 2003 study

reported on the incidence of rupture in 186 of these women at 2 of the 3 MRI centers from the 2001 study who still had their implants, and who underwent a second MRI screening in 2001.

Hölmich, et al. (2003)[50] reported the results of self-administered questionnaires from the patients who underwent the first MRI screening 1999. The questionnaires were completed, on average, 1 year before this (first) MRI examination. Women with intact implants (N = 146 women) were compared with women with MRI-diagnosed ruptures (N = 92 women), and there were no statistically significant differences in self-reports of local breast symptoms or generalized symptoms in women with intact versus ruptured implants when adjusted for age, placement, and type of implant. Women with evidence of extracapsular rupture on MRI were, however, 6 times more likely to report breast hardness than women with intact implants (OR 6.3, 95% CI 1.7-23.5). Although not statistically significant, women with extracapsular rupture were 3 times more likely to report a connective tissue disease (OR 3.8, 95% CI 0.4-35.1), 2 times more likely to report pleuritis (OR 2.2 95% CI 0.1-39.4), and 1.7 times more likely to report fatigue (OR 1.7, 95% CI 0.5-5.9) than women with intact implants, when adjusted for age, placement, and type of implant.

In 2004, Hölmich, et al.[51] reported that of 96 implants definitely ruptured at the first serial MRI in 1999, 19 (20%) were extracapsular and 77 (80%) were intracapsular. Among the 19 implants in 14 women with extracapsular silicone noted at the first MRI, the extracapsular silicone appeared to remain stationary in 16 implants, appeared to effuse marginally in one implant in one patient, and appeared to effuse significantly in 2 implants in one woman. This latter woman with significant extracapsular silicone gel effusion noted on the second compared to the first MRI, reported intermittent pain in the left lateral area. Explant surgery in this latter patient confirmed significant effusion of extracapsular silicone. Neither of the 2 women with effusion of extracapsular silicone reported any trauma.

Of the 77 intracapsular definite MRI ruptures at the first MRI screening in 1999 reported in Hölmich, et al. (2004), 69 (90%) showed no changes at the subsequent MRI screening in 2001. Of the 8 implants (10%) which showed a change between the first and second MRI screening, 1 which was suspicious for extracapsular silicone was actually a herniated capsule and all gel was reported to be intracapsular at explant. Of the remaining 7 implants suspicious for progression from intracapsular to extracapsular gel on MRI, all implants did, indeed, have evidence of extracapsular rupture at the time of explant. Three of these 7 women reported trauma to the affected breast between the first and second MRI examination, and one woman reported mammography.

The authors also reported the serologic findings and self-reported symptoms of a cohort 206 Danish women (405 implants) who had augmentation implants implanted between 1973 and 1998 (median duration of implantation 12 years; range 3 to 25 years), who still had their original implants, who had two serial MRI examinations in 1999 and in 2001, and whose implants were either intact at the time of both MRI examinations (N = 98 women with 193 implants) or who had at least one implant read as definitely ruptured at the first MRI screening in 1999 (N = 64 women with 96 implants). It is these two groups of women: intact (98 women with193 implants intact at both MRI screenings) and ruptured (64 women with 96 implants with at least one

definitely ruptured implant at the first MRI in 1999) which were compared for self-reported local breast symptoms and autoantibody status. With respect to autoantibodies, women with ruptured implants were not more likely to test positive for autoantibody tests such as ANA, RF, and ACL. Patients whose implant ruptures progressed from intracapsular to extracapsular did not have progression of autoantibody production. Women with ruptured implants were 2 times more likely to report non-serious pain to the affected breast (odds ratio 2.2; 95% CI 1.2 to 4.2) compared to women with intact implants. Women with ruptured implants were 2.5 times more likely to report a change in breast shape (OR 2.5; 95% CI 1.3-4.8).

The authors concluded that among 11% of ruptured implants, there appeared to be progression of silicone seepage, with some instances attributable to trauma while others seemed spontaneous. They believe that "intracapsular/extracapsular implant rupture is not a permanent condition and that the fibrous capsule, although solid and sometimes even calcified, is not impermeable to silicone." The authors also assert that untreated silicone rupture may entail the risk of silicone migration, which can remain unnoticed in many cases, but which can cause or increase capsular contracture and development of silicone granulomas.

5. Other Literature

Mentor referred to the literature for the questions of frequency of intracapsular gel, frequency of extracapsular gel, frequency of migrated gel and destination of migrated gel, frequency of intracapsular and extracapsular gel and gel migration beyond breast tissue, local complications associated with implant rupture, progression of silent to symptomatic ruptures, and progression of intracapsular to extracapsular ruptures. These references describe, for the most part, small case series of implants, and in some cases use mammography, which is inferior to MRI, for determining rupture status. Additionally, these references are not specific to Mentor's devices and are, therefore, of limited value in estimating the rupture rate for the implants in this PMA.

The literature cited described local complications of ruptured breast implants as silicone granuloma, axillary adenopathy, pain or tenderness, arm or neck pain, chest wall pain, breast size change, breast deformity, itching, joint swelling, and myalgia. There are reports of the presence of silicone using spectroscopy, in the surrounding capsule, axillary lymph nodes, and liver of women with intact implants.

Brown, et al. (2000)[52] studied a cohort of 344 women with 687 implants from a NCI study who under went MRIs. The median implant age was 16.4 years (range 6.4 to 28.0 years). Of the 687 implants, 378 (55%) were definite for rupture via MRI and 50 (7.2%) were indeterminate for rupture. Extracapsular ruptures were found in 85 of the 678 implants (12.4%) and involved 73 of the 344 women (21%).

Another study in which 90 women with 142 silicone gel-filled breast implants underwent MRI to detect implant rupture status, ANA testing, rheumatic symptom reporting, and magnetic resonance spectroscopy (MRS) to determine the presence of silicone in the liver, was reported by Gaubitz, et. al. (2002).[53] The mean duration of implantation was 9 years (range 1-26 years) with 24% of the women having implants for cosmetic reasons and 76% for reconstructive reasons. Twenty-four of the 90 women had implant rupture (27%) with 11 of the 90 women with evidence of extracapsular rupture on MRI (12% of the women; 46% of the 24 ruptures). Thirteen of the 24 women with ruptured implants (54%) had evidence of silicone in the liver,

compared to 15 of 51 women without implant rupture (23%), which was statistically significant (p=0.006). The authors believe that the positive MRS noted in women with intact implants could be due to gel bleed. Compared to a comparison group of 113 women without implants (62 with a history of breast cancer and 51 with hormone replacement therapy), there were no differences in ANA positivity for the entire group of 90 women with implants. For the patients with evidence of silicone in the liver via MRS, statistically significantly higher levels (p=0.033) of ANA positivity were noted (13 of the 28 MRS positive patients) compared to MRS-negative women (15 of 62). With respect to self-reported rheumatic disease symptoms, there were no statistically significant differences between women with intact versus ruptured implants. However, patients with MRS evidence of silicone in their livers complained more frequently of tingling and numbness in the fingers compared to women without MRS evidence of silicone in the liver.

In summary, besides the articles published using the Danish data summarized in items 3 and 4 above, the literature provides limited information on silent rupture progression to symptomatic rupture, intracapsular rupture progression to extracapsular rupture, and health consequences of rupture.

6. Summary

FDA conveyed three main issues with regard to rupture in the 4/14/04 major deficiency letter:

(1) What is the rupture rate over the lifetime of the device?

(2) When an implant does rupture, what is the incidence of intracapsular, extracapsular, and migrated gel, and what is the progression from intracapsular to extracapsular to migrated gel?

(3) What are the health consequences of implant rupture?

Mentor provided information from their Core Study, the Sharpe and Collis study, Danish literature data, and other literature to address these rupture issues.

Regarding the Mentor's Core Study data:

- The data consists of complete 2-year and partial 3-year data, and Mentor did not use these data to address the rupture rate over the lifetime of the device.

- The data are of limited value to address the local health consequences of rupture due to the small number of ruptures observed.

- The majority of silicone gel-filled breast implant ruptures are silent and detected only via MRI.

- Based on the MRI Cohort from the Mentor Core Study, the by-patient 3-year rupture rates are 0.5%, 0.8%, and 4.8%, respectively for augmentation, reconstruction, and revision patients. This rate excludes ruptures that were noted on microscopic evaluation but not at time of explant. This rate also excludes implants in which rupture was noted at the first but not the second MRI.

Regarding the Sharpe and Collis Study data:

- The study showed a by-implant point prevalence of rupture is 5.4% for implants with a median duration of implantation of 8.8 years (range 4-12 years). This point prevalence is limited to augmentation patients who were asymptomatic, who had no capsular contracture, who had no other surgical procedures, and who had textured implants placed only in a subglandular position by one surgeon. This rate also excludes implants removed within the first 4 years. Therefore, this point prevalence is probably an underestimation of that for the augmentation patients as a whole.

- Point prevalence of rupture does not characterize rupture rate over time.

- It is also not clear how these augmentation data could be used to estimate the rupture rate and rate over time for reconstruction and revision indications.

- There are differences in surgical procedures from that in the Mentor Core Study.

Regarding the Danish literature data:

- The Danish literature data are currently a major source of information to characterize the incidence of intracapsular rupture and extracapsular rupture, the progression of intracapsular rupture to extracapsular rupture, and the local health consequences of implant rupture. However, it does not completely address all the health consequences of rupture.

- It includes data from several manufacturers and is not specific to Mentor implants.

- It provides information on the prevalence and incidence (over 2 years) of augmentation implant rupture; however, it is of limited value to characterize the rupture rate and rate over time of the Mentor implants because the data are not specific to the Mentor implants.

- For augmentation implants with a median duration of implantation of 12 years (range 3-25 years) which were not explanted in at least the first 3 years, the point prevalence of rupture is 36% if both definite and possibly ruptured implants are considered.

- The proportion of extracapsular ruptures of the total is approximately one-fourth.

- There is progression of silicone seepage in 11% of ruptured implants within 2 years, with some instances attributable to trauma while others seemed spontaneous.

- Approximately 10% of intracapsular ruptures progress to extracapsular rupture in 2 years.

- Women with evidence of extracapsular rupture on MRI were 6 times more likely to report breast hardness than women with intact implants (OR 6.3, 95% CI 1.7-23.5). Although not statistically significant, women with extracapsular rupture were 3 times more likely to report a connective tissue disease (OR 3.8, 95% CI 0.4-35.1), 2 times more likely to report pleuritis (OR 2.2 95% CI 0.1-39.4), and 1.7 times more likely to report fatigue (OR 1.7, 95% CI 0.5-5.9) than women with intact implants, when adjusted for age, placement, and type of implant.

- Women with ruptured implants were 2 times more likely to report non-serious pain to the affected breast (odds ratio 2.1; 95% CI 1.2 to 4.2) compared to women with intact implants.

- The Danish literature data describes a rupture incidence rate for definite or possible ruptures of 8.9 ruptures per 100 implants per year (95% confidence interval 6.6 – 11.3). Based on the ASPS website, there were about 250,000 augmentation patients voluntarily reported as having breast augmentation just in the year 2003, with an average increase of 10% per year since 2000. Assuming that augmentation patients have bilateral implants at the incidence reported in 2003, that would be 500,000 augmentation implants per year. If half of the augmentation mammoplasties reported in 2003 would be with gel-filled implants if approved (this is probably an underestimation), there would be 250,000 silicone gel-filled augmentation implants per year. Of these 250,000 silicone gel-filled implants per year, using the Danish literature data (i.e., 9 ruptures per 100 implants per year), one could expect at least 22,500 implant ruptures per year in augmentation patients.

Regarding other literature:

- In addition to the Danish literature data, there are case reports in other literature describing health consequences of rupture. However, this literature does not completely address all health consequences of rupture, and the literature is not specific to Mentor implants.

K. ADJUNCT STUDY CLINICAL DATA

Mentor's Adjunct Study is an ongoing 5-year study designed to address the public health need of reconstruction and revision patients. Mentor's Adjunct Study was approved in 1992. Safety data includes complications, rheumatology questionnaire, types of surgical procedures, and reasons for removal. The evaluation timepoints are 1, 3, and 5 years. There is no limit on the number of patients, investigators, or sites, all of which are being continuously enrolled. The Adjunct Study does not include an MRI cohort; therefore, silent rupture cannot be evaluated.

Mentor has a single Adjunct Study that includes 3 different types of Mentor silicone gel breast implants:

- Low Bleed Gel-filled Mammary Prosthesis (P910037)
- Becker Expander/Mammary Prosthesis (P910038)
- Combination Gel-Saline Mammary Prosthesis (P910036) – Mentor is no longer manufacturing this device and withdrew P910036 in 12/97.

For the purposes of this PMA, Mentor provided data specific to only the Low-Bleed Gel Mammary Prosthesis. As a note, ≈90% of the devices implanted in the Adjunct Study are for the subject Low Bleed Gel implant.

The data provided are cumulative from 9/92 through 11/02 with a date of database closure of 9/29/03.

1. Patient Accounting

The indications in the Mentor Adjunct Study are defined as follows:

- **Reconstruction** - reconstructive mammaplasty on a breast that has not undergone prior mammaplasty, following mastectomy or other cancer treatments requiring reconstruction, as well as reconstructive mammaplasty to correct post-trauma deformities, congenital or developmental deformities, severe ptosis correctable by mastopexy, or medical or surgical complications resulting in severe breast deformity

- **Revision** - correction of complications or unfavorable results of a reconstruction surgery, as well as medically necessary replacement of existing breast implant originally placed for augmentation, when saline-filled implants are not suitable as replacement.

From 9/92 through 11/02, 44,951 patients (with 87,106 devices) were enrolled in the Adjunct Study. The follow-up rates were 18-19% at 3 years and 10-11% at 5 years. Patients are being continuously enrolled into the study; therefore, the patient accounting tables do not have the typical cumulative presentation. The tables below are the patient accounting data for each indication, based on the 9/03 date of database closure.

Adjunct Study Revision Patient Accounting	Baseline	Year 1	Year 3	Year 5
Theoretically Due	34,205	28,420	20,902	13,336
Deaths	0	0	0	0
Patients with devices explanted without replacement	0	543	121	95
Patients with devices explanted with replacement	0	1064	248	174
Expected Due	34,205	27,877	20,781	13,241
Discontinuations*	0	18,212	17,009	11,878
Actual	34,205	9665	3772	1363
% Follow-up	100%	35%	18%	10%

*Discontinuations were computed by subtracting actual count from expected due.

Adjunct Study Reconstruction Patient Accounting	Baseline	Year 1	Year 3	Year 5
Theoretically Due	13,288	10,714	6740	3600
Deaths	0	0	0	0
Patients with devices explanted without replacement	0	216	47	43
Patients with devices explanted with replacement	0	365	91	65
Expected Due	13,288	10,498	6693	3557
Discontinuations*	0	6884	5392	3163
Actual	13,288	3614	1301	394
% Follow-up	100%	34%	19%	11%

*Discontinuations were computed by subtracting actual count from expected due.

Given that the percent follow-up is so low for these 2 indications, the Adjunct Study data are difficult to evaluate. Because MRIs were not performed in the Adjunct Study, these data are of no value in determining the rupture rate and the rate over the lifetime of the device. Thus, only the primary safety dataset of KM risk rates is presented below.

2. KM Risk Rates

Mentor provided KM risk rates through 1, 3, and 5 years based on the first report date for each complication type as the time to first occurrence was not known. For both indications, asymmetry, breast pain, capsular contracture III/IV, explantation, reoperations, and wrinkling had the highest rates.

By-patient, KM cumulative risk rates (95% CI) of complications per indication for Adjunct Study						
Complication	**Revision**			**Reconstruction**		
	1 Yr N=15,679	**3 Yrs N=5743**	**5 Yrs N=1595**	**1 Yr N=5588**	**3 Yrs N=1820**	**5 Yrs N=468**
Asymmetry	7% (7, 8)	19% (18, 20)	28% (27, 29)	10% (9, 11)	27% (26, 29)	43% (41, 46)
Breast pain	4% (4, 5)	13% (13, 14)	20% (19, 21)	4% (3, 4)	12% (11, 13)	19% (17, 21)
Calcification	0.2% (.1,.3)	0.8% (.6, 1)	1% (1, 2)	0% (0, .1)	0.4% (.1, .8)	1% (.2, 2)
CC, III & IV	4% (4, 5)	12% (11, 12)	19% (18, 20)	3% (3, 4)	10% (9, 11)	16% (14, 19)
Delayed wound healing	0.6% (.5,.8)	1% (1, 1)	1% (1, 1)	1% (1, 1)	2% (2, 3)	3% (2, 4)
Extrusion	0.4% (.3,.6)	0.8% (.6, 1)	1% (.7, 1)	1% (.8, 1)	1% (1, 2)	1% (1, 2)
Hematoma	1% (.9, 1)	2% (1, 2)	2% (2, 2)	0.8% (.5, 1)	1% (.8, 1)	1% (.8, 1)
Hypertrophic scarring	1% (1, 1)	4% (4, 5)	6% (5, 6)	1% (1, 2)	6% (5, 7)	8% (7, 10)
Infection	1% (1, 1)	2% (1, 2)	2% (1, 2)	1% (1, 1)	2% (1, 3)	2% (2, 3)
Irritation / inflammation	1% (1, 1)	3% (2, 3)	4% (3, 4)	1% (1, 1)	2% (1, 3)	3% (2, 4)
Lymphadenopathy	0.3% (.2, .4)	1% (.9, 1)	2% (1, 2)	0.2% (.1, .3)	0.7% (.3, 1)	1% (.7, 2)
Necrosis	0.2% (.1, .3)	0.5% (.3, .7)	0.7% (.4, 1)	0.9% (.6, 1)	1% (1, 2)	1% (1, 2)
Explantation	8% (7, 8)	10% (10, 11)	13% (12, 14)	8% (7, 9)	11% (10, 12)	13% (12, 15)
Reoperations	2% (2, 3)	6% (6, 7)	10% (9, 11)	4% (4, 5)	13% (12, 15)	19% (16, 21)
Rupture (symptomatic)	0.6% (.4, .7)	0.9% (.7, 1)	1% (1, 2)	0.3% (.1, .4)	0.6% (.3, .9)	2% (.5, 4)
Seroma	1% (.8, 1)	1% (1, 2)	2% (1, 2)	0.8% (.5, 1)	1% (.9, 1)	1% (.9, 1)
Wrinkling	5% (4, 5)	19% (18, 20)	27% (26, 29)	4% (3, 4)	15% (14, 17)	27% (24, 30)

L. SUPPLEMENTAL LITERATURE INFORMATION

As information intended to supplement their Core Study, Mentor provided a summary of the literature on the topics of:

- CTDs, including fibromyalgia
- cancer and benign breast disease
- 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 gel and migrated gel rupture
- suicide risk.

FDA has previously performed its own review of the published literature, which was not specific to any sponsor, on the topics above. In addition, FDA performed a literature search with PubMed to identify literature published since the October 2003 Panel meeting. FDA identified few new articles on the topics above. Although these new articles add to our knowledge on these topics, there are no new issues raised for which we seek Panel input.

For the literature published since the IOM Report, refer to Mentor's CD for their summary of the published literature (Mentor's CD is provided in Tab 4 of your Panel package). FDA also refers you to Mentor's labeling, which includes Mentor's proposed wording on these issues (a copy of Mentor's draft labeling is provided in Tab 3 of your Panel package). The FDA Breast Implant Consumer Handbook also includes a discussion on the topics of cancer, CTD, mammography, neurological disease, breast feeding (ability to lactate), effects on children (safety of milk for breastfeeding and 2nd generation effects), and suicide, which were based on our review of the literature. A copy of the handbook is available through FDA's website at http://www.fda.gov/cdrh/breastimplants/indexbip.html. As a note, literature studies related to local health consequences of rupture are discussed in Section J (**Rupture Rate and Health Consequences**) above.

For completeness sake, FDA is providing you with the following summary of the literature published since the October 2003 Panel meeting based on our own PubMed search. No new articles on the topics of neurological disease or potential systemic health consequences were identified.

CTD

The published epidemiologic literature following the IOM report[54] does not support an association of breast implants and CTD. This literature cannot, however, completely address rare diseases, such as CTDs. Although there are references which suggest that there may be a subset of women with breast implants who may be more susceptible to having FM, the characteristics which define this subset has not been defined, and these findings have not been confirmed. Of note, both the Danish and Swedish literature data indicate that women with implants report greater frequency of some rheumatic symptoms compared to women with other cosmetic surgery; however, a consistent pattern of symptom reporting has not been reported. Below is a summary of the recently published studies.

Kjøller, et al.[55] evaluated self-reported rheumatic symptoms via questionnaire in 423 women who received cosmetic breast implants from 1977 to 1997 at 2 of the clinics in Denmark, comparing them to 231 women other types of cosmetic surgery and to183 women from the general Danish population as in the earlier study. While there were no statistically significant increases in symptoms when grouped by frequency (i.e. mild = 1 to 3 symptoms, moderate = 4-6 symptoms, and severe = >6 symptoms), there were statistically significantly higher reports of joint stiffness in women with implants compared to both women with other cosmetic surgery and the general population. There were also statistically significantly higher reports of finger swelling in women with implants compared to women with other cosmetic surgery. There were no statistically significant increases in fatigue in women with implants compared to the other two groups. It should be noted that only 56% of the women with implants, 35% of the women with other cosmetic surgery, and 47% of the general population returned the questionnaire.

Six months after the Kjøller publication above, some of the same authors (Breiting, et al.[56]) reported the results of a self-administered questionnaire, blood testing for autoantibodies, and a clinical examination of the breasts for women with implants, also Danish literature data. There were 190 women with breast implants, 186 women with breast reduction, and 149 general population controls who participated. Compared to population controls, women with breast implants reported significantly greater fatigue, Raynaud-like symptoms (white fingers and toes on exposure to cold), and cognitive difficulties. Self-reported use of hormone replacement and use of psychotropic drugs, particularly antidepressants, was also reported to a greater frequency in women with breast implants compared to both control groups. Women with breast implants were also more likely to report breast pain than were women who had undergone breast reduction. With respect to autoantibodies, there were no significant differences with respect to ANA, RF, and IgG anticardiolipin antibody. However, significantly greater levels of IgM anticardiolipin antibody were found in women with implants (OR 9.6; 95%CI 1.2 to 76.2) compared to both control groups. It should be noted that only 52% of the women with implants, 50% of the women with breast reduction surgery, and 41% of the general population contacted participated in this study.

Another publication of the Danish literature data from Hölmich, et al.[51] (2004) compared the results of questionnaires focusing on breast symptoms and autoantibody status in women with ruptured implants by MRI and women with intact implants on MRI. This study was also summarized earlier in Section J (**Rupture Rate and Health Consequences)**. With respect to autoantibodies, women with ruptured implants were not more likely to test positive for autoantibody tests, such as ANA, RF, and ACL. Patients whose implant ruptures progressed from intracapsular to extracapsular did not have progression of autoantibody production.

Another population based study of a random sample of women in the Swedish national implant registry who had cosmetic breast augmentation during 1965 and 1993 (n = 1536) was compared with a sample of women who had breast reduction surgery during the same period (n = 2496), who were sent an questionnaire or completed a telephone interview assessing for rheumatologic signs and symptoms (Fryzek, et.al.[57]). A significant proportion of women with implants (65%) and women with breast reduction (72%) completed the questionnaire. After adjusting for age, history of any pregnancy, history of ever smoking, current alcohol consumption, and body mass index, and after excluding patients with missing dates of onset of symptoms, the following symptoms were reported with statistically significantly greater frequency in implanted women

compared to controls: painful joints more than 3 months, muscle pain more than 3 months, persistent or recurrent muscle weakness, recurrent sensation of sand or gravel in eyes, dry mouth for more than 3 months, difficulty swallowing, unexplained fever, skin redness on both cheeks, other skin abnormalities, tingling and numbness, persistent or recurrent neck ache, persistent or recurrent shoulder ache, persistent or recurrent back ache, abnormal fatigue, depression, difficulty finding words, and hair loss. After excluding patients with chronic disease following surgery, the following symptoms remained statistically significantly higher in breast implant recipients: painful joints more than 3 months, muscle pain more than 3 months, persistent or recurrent muscle weakness, recurrent sensation of sand or gravel in eyes, unexplained fever, skin redness in both cheeks, other skin abnormalities, tingling and numbness, persistent or recurrent neck ache, persistent or recurrent shoulder ache, persistent or recurrent back ache, abnormal fatigue, depression, difficulty finding words, and hair loss. In most of these, the relative risk was between 1 and 2. For the symptoms of recurrent sensation of sand or gravel in eyes and unexplained fever, the relative risk was greater than 2.

A retrospective cohort study performed by the NIH[58] of self-reported CTD diagnoses was performed on women with cosmetic breast implants implanted between 1960 and 1996 at one of 18 plastic surgery practices in the U.S. A comparison group of other cosmetic surgery patients at these same practices was also assessed for self-reported CTD diagnoses. There were 7,234 (71%) implanted women and 2,138 (72%) control women who completed the questionnaires. Significant risk elevations were noted all CTD diagnoses in breast implant recipients compared to controls, except multiple sclerosis, with highest risks noted for Sjögren's syndrome, scleroderma, and Raynaud's phenomenon. To evaluate reporting bias, the authors analyzed CTD diagnosis reporting before and after 1992, when FDA changed the status of implants to investigational. They found significant elevations in reporting both before and after 1992 for the diseases of rheumatoid arthritis, scleroderma, Sjögren's syndrome, Raynaud's phenomenon, and chronic fatigue syndrome for breast implant recipients compared to controls. In an attempt to confirm the diagnoses of rheumatoid arthritis, scleroderma, and Sjögren's syndrome, the patient records were retrieved and reviewed for 56% of the breast implant patients and 66% of the control patients who had completed the questionnaire. After deriving estimates of the risk for all patients based on the risk from patients with retrieved records, the authors estimated a risk of 2.0 (95% CI: 0.7, 5.4) for the three diseases of rheumatoid arthritis, scleroderma, and Sjögren's syndrome, and 1.3 (95% CI: 0.5, 3.8) for rheumatoid arthritis, findings which were no longer statistically significant. The authors suggest that, based on their sample size, in order to rule out a smaller risk for CTD (and especially for rare diseases such as scleroderma and Sjögren's syndrome), future studies would need to be very large.

The recently published review by Lipworth, et al.[59] examined the 6 published epidemiologic studies - including the Danish and Swedish studies discussed above - which have evaluated the risk of fibromyalgia and breast implants, concluding that the weight of the epidemiologic studies do not support an association between fibromyalgia and breast implants.

Cancer and Benign Breast Disease

McLaughlin and Lipworth[60] reviewed previously published studies on the issue of brain cancer and breast implants and cited an unpublished observation from a Los Angeles study of 3182 women with cosmetic breast implants (Deapen, et al.) describing an SIR of 1.64 (95% CI, 0.3-4.8) for brain cancer.

Device Interference with Mammographic Detection

Previously published studies on the impact of breast implants on mammographic detection have indicated that breast implants interfere with mammographic imaging. As a result of issues with detection, radiologists now use displacement techniques to move the breast implant out of the way and image tissue. A newly published paper by Miglioretti, et al.[61] on the effect of breast augmentation on the accuracy of mammography in women with breast implants compared a prospective cohort of 137 women with breast augmentation to 685 women without breast implants with breast cancer to matched women with breast implants or without. In this study, characteristics of the cancer in these two groups of women with cancer were compared (stage, nodal status, size, grade, estrogen-receptor status). The study indicated that both sensitivity and specificity of screening were lower in women with implants but that for women with cancer, stage at diagnosis, size, estrogen-receptor status, and nodal status were similar. They concluded that the prognostic characteristics of tumors were not different in women with breast implants.

The other study published on breast implants and mammography was FDA's study of medical device reports on this issue.[62] This study identified 66 adverse event reports on women with breast implants related to mammography. The majority of these reports, 41/66 (62.1%), described possible breast implant rupture during mammography. Other adverse events reported included mammographic compression crushing implants, pain during mammography attributed to implants, inability to perform mammography because of capsular contracture or fear of implant rupture, and delayed detection of cancer attributed to implants.

Lactation and Breast Feeding

One new case series by Hill, et al.[63] describes two women with breast implants who were unable to express adequate milk for their preterm infants. Both women were enrolled in a study to evaluate milk volume over time in mothers with preterm infants. The research program involved using a breast pump to establish an abundant milk volume for their preterm infant when breastfeeding becomes feasible. In both cases, implanted mothers were unable to establish an adequate milk supply for their preterm infants. *This was a case series so no conclusions may be drawn about the relationship between implants and breast feeding. There are other reasons that women with preterm infants may be unable to establish an adequate milk supply.*

Offspring Issues

A study by Hemminki, et al.[64] of postimplant childbearing issues in Finland found that 26% of their cohort had one or more children after mammoplasty. Women who had children after implantation had their first post-implant child an average of 4.7 years after implantation. Twenty control infants born the same year to mothers without implants were identified from the Finnish Medical Birth Register for each infant of women with breast implants (born after implantation). Analysis was controlled for mother's age, social class, residence, previous births, smoking status, and other relevant variables. Their findings were that there were more infants with instrumental

delivery (vacuum or forceps) among controls. Other differences were that women with implants were more likely to have had previous pregnancies ending in spontaneous or induced abortion and infants of women with implants were smaller when mothers were multiparous. There was a higher frequency of diagnosed breech or other abnormal positions of babies delivered by the implant group. However, it is difficult to draw conclusions on this study based on the small sample size.

Suicide Risk

At the time of the October 2003 Panel meeting, three studies found an increased rate of death by suicide for women with breast implants than comparison populations. Since that time, an additional study by Jacobsen, et al.[65] has supported this finding. This cohort study compared mortality experience of 2761 Danish women with cosmetic breast implants to the general female population. Women with cosmetic implants had significantly elevated standardized mortality ratios (SMR) for death overall (SMR 1.4, 95%CI 1.1-1.7), for non-malignant lung disease (bronchitis, emphysema, asthma and unspecified chronic obstructive pulmonary disease) (SMR 3.4, 95%CI 1.4-6.9), and for suicide (SMR 3.1, 95%CI 1.7-5.2). Women who underwent breast implant surgery also reportedly had a significantly higher prevalence of psychiatric admissions prior to cosmetic surgery compared with women who underwent breast reduction or other cosmetic surgeries.

Another study of Danish women by Breiting, et al.[66] compared the use of antidepressants, anxiolytics, and hypnotics by women with implants vs. women with breast reduction, as well as women with implants vs. population controls. Compared to women with breast reduction, women with breast implants were more likely to report the postoperative use of antidepressants (OR 6.7, CI 2.3-19.7). Compared to population controls, women with breast implants were more likely to report the postoperative use of antidepressants (OR 5.2, CI 1.8-15.4) and hypnotics use (OR 5.0, CI 1.1-22.6). The authors also looked at women with one breast implantation surgery, as well as women with two or more breast implantation surgeries. The women with two or more breast implantation surgeries were even more likely to report antidepressant use than women with one breast implantation surgery compared to women with breast reduction or compared to population controls. Refer to summary table below from this reference.

Psychotropic Drug	**Women with 1 Implantation Surgery (N=114) versus**		**Women with 2 or More Implantation Surgeries (N=76) versus**	
	Breast Reduction	**Population Control**	**Breast Reduction**	**Population Control**
Antidepressant	5.9 (1.9-18.6)	4.6 (1.5-14.4)	8.9 (2.7-28.7)	6.8 (2.1-21.7)
Anxiolytic	1.6 (0.8-4.3)	2.4 (0.8-7.4)	2.0 (0.7-5.6)	2.9 (.9-9.4)
Hypnotic	1.1 (0.4-3.1)	4.0 (0.8-20.3)	1.7 (0.6-4.9)	6.6 (1.3-33.6)

The above studies demonstrate a statistical association, but do not prove a causal relationship between breast implants and suicide risk.

M. MENTOR'S COMPLAINT ANALYSIS

Mentor provided an analysis of reported complaints received over the last 18 years. Of the 314,922 Mentor silicone gel-filled breast implants sold domestically from 1985 through 9/30/03, they received 8060 complaints. Of the 8060 complaints, 4219 had devices returned for analysis. Of these 4219 devices, 1714 were classified as "no abnormality" (i.e., no visible flaw or abnormality) and 2505 were classified with observed abnormalities. All devices involved were either devices on the market prior to May 1976 (i.e., preamendments) or those from the Adjunct Study.

Mentor provided a summary of the observed abnormalities for the 2505 devices; however, these were based on only visual observations. The primary observed abnormalities were rents at 60% and iatrogenic failure at 25%. Failures that were categorized as a rent when there was a visible opening of the shell and no parallel striations were observed. Although, 60% of the observed abnormalities were categorized as rents, these openings may be attributable to multiple sources which were not further defined and categorized in this analysis. Failures were categorized as iatrogenic when parallel striations on the edges of the rent were observed.

Mentor provided post-implantation complaints from 1985 through 9/30/03 for the 2505 confirmed abnormalities as compared to all devices in the complaint database. The most reported complication for the 2505 devices with observed abnormalities was rupture/leakage (66%), followed by tear/hole (11%) and capsular contracture (6%).

Mentor also provided the complaint data based on year of complaint and the number of years in-vivo for the device, including that for rupture/leakage through 18 years. However, no conclusions, such as rupture rates over time, can be made regarding these data because of the method of collecting and reporting the data to the complaint analysis. Accordingly, these data are not summarized in the Panel memo.

Mentor's complaint analysis provides little supplemental information to the existing clinical data.

N. FDA'S MEDWATCH

MedWatch is FDA's device reporting system. MedWatch databases consist of voluntary reports by the public and mandatory medical device reports (MDRs) by manufacturers, importers, distributors (until 2/98), and user facilities. The table below describes each of the MedWatch databases/collection systems.

Database/ Collection System	Description	Data Includes	Reported By
Device Experience Network (**DEN**)	DEN database serves as a historical database for reports. User facilities are listed under voluntary reporting for the DEN because mandatory requirements for user facility reporting under the SMDA 1990 were not in effect prior to 7/31/96, so user facilities were encouraged to voluntarily report. DEN does not contain device or patient problem codes and cannot be searched on many data fields, including implant and explant dates. DEN uses causative factor codes.	Voluntary reports of patient and device problems from 1/1/78 to 5/31/93.	Consumers, health professionals, and user facilities
		Mandatory MDR reports of device malfunction and serious injury or death associated with the device from 12/1/84 to 7/31/96.	Manufacturers
Manufacturer and User Facility Device Experience (**MAUDE**)	MAUDE is the predominate database used by FDA for evaluation of individual device-related adverse event reports. MAUDE is the only database with implant and explant dates. It also had device and patient problem codes, and manufacturer evaluation and conclusion codes. As a note, DEN and MAUDE may include several report sources for one event. For example, one incident may have been reported as a voluntary report by a consumer, a physician, or an attorney, and reported as a mandatory report by a manufacturer, a user facility, or an importer. The databases will link same reports.	Voluntary reports of patient and device problems from 6/1/1993 to present.	Consumers and health professionals
		Mandatory MDR reports of device malfunction and serious injury or death associated with the device from 7/31/96 to present.	Manufacturers, distributors, and importers
Alternative Summary Reporting Program (**ASR**)	ASR database contains manufacturer summary reports submitted on a quarterly basis of approved adverse events (usually adverse events that are well-known in the scientific and medical literature). For breast implants, the adverse events include rupture, leaks, deflation/inflation, wrinkling, capsular contracture, and non-specific complaints. In October 1999, new requirements for ASR program started. Manufacturers now provide patient and device codes as well as evaluation and conclusion codes for each adverse event. Summary reports do not contain narrative text. Implant and explant data are not captured in ASR.	Mandatory MDR reports of device malfunction and serious injury associated with the device from 1995 to present. Deaths are still reported through MAUDE except for cardiac heart valves.	Manufacturers

FDA performed a search on Mentor's silicone gel breast implants through the MedWatch databases: DEN, MAUDE, and ASR. Each database has its unique features in terms of the type of data collected. Also, it should be noted that there may be duplicate reports across the databases. FDA performed a search on all silicone gel breast implants for comparison purposes. Although the time period for each database is different, the overall search time period is 1/1/84 through 12/31/03.

As of 12/31/03, FDA received a total of 135,174 reports across all silicone gel breast implant manufacturers. Of those, 9,292 (7%) were Mentor's silicone gel breast implants. The table below shows the number of reports for each of the databases.

Silicone Gel Breast Implant Reports, 1/1/84–12/31/03		
Database	**Total Reports**	**Mentor Reports**
DEN 1/1/84 – 12/31/97	96,954	4557 (5%)
MAUDE 1/1/92 – 12/31/03	14,121	564 (4%)
ASR 4/1/95 – 9/30/02	24,099	4,171 (17%)
Total	**135,174**	**9,292 (7%)**

DEN

With regard to the DEN database (1984-1997), both adverse event reports and the associated "causative factors" reports were recorded. There were 593 causative factors reported by manufacturers on 96,954 adverse event reports associated with silicone gel breast implants. There were 128 causative factors reported on 4,557 adverse event reports by Mentor. The table below summarizes the DEN data for Mentor, including the rates of the top causative factors.

DEN, 1984-1997	
Mentor Adverse Event Reports	
Death	2
Injury	4,525
Malfunction	30
Other	0
Total	**4,557**
Rates of Mentor's Top Causative Factors	
	N=128
Incorrect technique/procedure	53.9%
Failure to follow instructions	15.6%
Inherent risk of procedure (immediate post-op)	9.4%
Known complication (long-term)	4.7%
Device	4.7%

MAUDE

With regard to the MAUDE database (1/1/92 – 12/31/03), there were 17,993 device problem codes and 42,018 patient problem codes submitted on 14,121 adverse even reports across all manufacturers. There were 890 device problem codes and 2,019 patient problem codes

submitted on 564 adverse event reports for Mentor. The table below summarizes the MAUDE data for Mentor, including the rates of the top device and patient problems.

MAUDE, 1/1/92 – 12/31/03	
Mentor Adverse Event Reports	
Death	2
Injury	384
Malfunction	68
Other	110
Total	**564**
Rates of Mentor's Top Device Problems	
	N=890
Explanted	42.7%
Rupture	30.4%
Unknown	18.0%
Migration	2.0%
Implant extrusion	0.9%
Rates of Mentor's Top Patient Problems	
	N=2,019
Pain	16.6%
Surgical procedure	13.7%
Capsular contracture	7.2%
Unknown	4.8%
Connective tissue disease	4.4%
Fatigue	4.3%

Additionally, of the 563 Mentor adverse event reports, 397 had implant and explant dates. Those data indicate that the median implant duration for Mentor implants, with associated adverse events reported only to MAUDE, was 4 years, and the average implant duration was 5 years.

ASR

With regard to the ASR database, from 10/1/95 through 9/30/02, there were 24,099 adverse event reports submitted across all manufacturers, of which 4,171 (17%) were submitted by Mentor. In the current ASR program, which allows for more detailed entries, the search timeframe was 10/1/99 through 9/30/02.

There were 7,002 device problems submitted across all manufacturers. Mentor submitted a total of 2,259 device problems (32% of total). Mentor's top three reported device problems were "rupture," "other," and "tube(s), defective," which comprised ≈96% of the device problems. *It should be noted that the observations recorded under "tube(s), defective" are not applicable to the Mentor silicone gel breast implant under PMA review. Instead, these reports apply only to the Mentor Becker product, which is* not the subject of this PMA.

With regard to patient problems, there were 7,824 patient problems submitted across all manufacturers. Mentor submitted a total of 867 patient problems (11% of total). Mentor's top three reported patient problems were "capsular contracture," "infection," and "pain," which comprised ≈84% of the patient problems.

O. MENTOR'S POSTAPPROVAL PLANS

Mentor provided a description of the following postapproval plans, should their PMA be approved:

- Core postapproval study
- Patient registry
- focus group study of patient labeling
- physician education/training.

1. Core Postapproval Study

The purpose of a postapproval study is to collect long-term data on a device. Below is a brief summary of Mentor's proposed postapproval study plan for their Core Study. Mentor's postapproval protocol is a modification of their existing IDE study protocol. As per the current IDE study protocol, the patients will continue to be evaluated by their physicians annually through 10 years. The MRI cohort will also continue to include evaluations at the remaining 4, 6, 8, and 10-year timepoints. Mentor proposes no changes to the current protocol in terms of data collection. Mentor also stated that they do not believe it is necessary to follow patients after all study devices are explanted.

2. Patient Registry

Rather than initiate their own patient registry, Mentor stated that they will contract with the American Society of Plastic Surgeons (ASPS) and the Plastic Surgery Education Foundation (PSEF), who developed the Tracking Outcomes in Plastic Surgery (TOPS) registry. The TOPS collects plastic surgery procedural data and clinical outcomes. Embedded within the Internet data-collection tool of TOPS is the NaBIR registry (National Breast Implant Registry). NaBIR can track information, such as the number of implants placed or removed, clinical indications, type of facility, anesthesia administered, and short-term complications. The registry was designed to allow physicians to track implanted devices. Mentor does not have direct access to the NaBIR database, but can request reports from the TOPS/NaBIR registry databases. They have proposed that it will be funded using a patient pass-through fee to NaBIR (i.e., both the patient and Mentor absorb the costs).

Mentor stated that plastic surgeons who are participating in the TOPS registry will ask the patients to participate in NaBIR. If the patient agrees, the physician will enter patient and surgery specific information in the TOPS database at the time of initial surgery and completes the TOPS form. The TOPS form is also completed at patient follow-up visits, where outcome data are recorded including complications. With regard to safety data, the TOPS form is essentially limited to the choices of delayed wound healing, infection, seroma, wound infection, hematoma, and unplanned reoperation. After completion of the TOPS form, the NaBIR form, specific to breast implant procedures, is completed. The NaBIR form captures standard initial surgery information, the number of in-vivo years, and the reason for removal. CTD data are not collected on the TOPS or NaBIR forms. Postoperative data are collected only when the patient returns for a follow-up visit. There are no preset evaluation timepoints.

Although Mentor provided a description of what data are collected in the proposed TOPS and NaBIR registries, Mentor did not provide their plans for analyzing the data.

3. Focus Group Study

The overall purpose or goal of a focus group study is to improve the quality of the patient labeling. Mentor provided a draft focus group study protocol.

The specific goals of the focus group study will be:

- to determine whether the brochure achieves its educational and informed decision objectives and, if not, how it should be revised to order to achieve them
- to assess whether the information in the brochure is clearly understood
- to identify unintended effects associate with the brochure exposure (e.g., inaccurate perceptions or problematic attitudes and beliefs)
- to assess the brochure's effectiveness in conveying the risks and benefits of implant use
- to obtain patient suggestions for improvements in the brochure
- to identify additional information needed by patients after they have read the brochure.

The focus groups will be conducted in person by an experienced professional contractor who will also summarize the results. Mentor proposed 4 focus group interviews, 2 for potential augmentation patients and 2 for potential reconstruction patients. Each group will have 8-10 patients. The interviews will take place at 2 sites.

Numerous questions will be asked of each respondent. The respondents will also be asked to identify suggested improvements in the brochure that have not identified during the discussion, as well as to identify other information they would like in order to make an informed decision. After the contractor has provided Mentor with the report, Mentor will revise the patient brochure to reflect the appropriate changes and/or suggestions.

A copy of the focus group study protocol is provided on Mentor's CD in Tab 4 of your Panel package.

4. Physician Education/Training

Mentor stated that they are working with the ASPS, PSEF, and the American Society of Aesthetic Plastic Surgeons (ASAPS) to develop a comprehensive physician training program. The objectives of the physician education program (**Silicone Breast Implant Education Symposium**) include:

- proper surgical technique with silicone gel implants
- appreciate accurate anatomic diagnosis and preoperative planning
- practice smart risk management in breast surgery
- improve the consultation, discuss staff involvement, manage patient expectations
- understand implant mechanical properties
- discern difference in demographic data of various implants and operations
- learn how to choose over vs. under muscle, smooth vs. textured, and silicone vs. saline
- diagnose and surgically treat implant rupture
- management of implant complications
- develop methods for long-term patient follow-up and comply with FDA guidelines.

Mentor stated that they have been collaborating on the presentations to ensure that the program content is comprehensive and will work on an on-going basis to update the slides, as needed. Mentor will also provide support materials for this training, such as product labeling and relevant literature. The symposiums will be conducted 5 times annually in conjunction with regularly scheduled society meetings, and will also be available on DVD and as an internet-based CME educational program for those physicians that may be unable to travel to these symposium.

Mentor's corporate website will also list the names and contact information for surgeons who have completed a Silicone Breast Implant Education Symposium. Mentor plans to require physicians to obtain a "Certificate of Participation" in the symposium prior to shipping the product.

With regards to modes and causes of rupture information, Mentor stated that they plan to provide scanning electron micrographs (SEMs) of the failure modes. With regard to rupture screening methods and frequency, only general information is provided in the slides. With regard to removal after confirmed rupture, the slides identify intracapsular rupture as a questionable clinical significance, but identify extracapsular rupture as a local complication requiring reoperation.

From the information provided, it appears that, while Mentor has been allowed to provide input on the content of the Silicone Breast Implant Educational symposium, it is not a meeting limited to the Mentor silicone gel product. This training does not appear to include any specific information with regard to rupture screening method and frequency or removal after confirmed intracapsular or extracapsular rupture, as well as modes and causes of rupture findings, which should be based on the Mentor data.

P. LABELING

In terms of a labeling/packaging overview, the implant is placed in an inner thermoform container which is sealed with a Tyvek lid. The inner thermoform is then placed inside another thermoform container (i.e., outer thermoform) and sealed with an outer Tyvek lid. There are 2 labels applied to the outer thermoform: (1) a small label is fixed to the side and contains information specific to the device lot number and serial number and (2) a large label is applied to the Tyvek lid and contained descriptive information about the device. The double-nested thermoforms are placed in a cardboard shipping insert which helps hold the thermoforms in place one inside the unit carton. The patient record labels and the Patient ID Card are placed inside the unit carton. The unit carton is closed and 2 labels are fixed to one end of the carton. One label is device specific information, and the other is a "Made in the U.S.A." label. The physician and patient labeling are the primary pieces of labeling for this product.

The **physician labeling** (or package insert) will be provided to the physicians electronically rather than inside the carton unit. It will also be made available for viewing or printing on the Mentor website (www.mentorcorp.com). An 800 number will be provided for physicians to request a copy of the package insert A label will be applied to the outer thermoform Tyvek lid, as well as the outside of the unit carton, directing the physician to the website and 800 telephone number.

The **patient labeling** (or Patient Informed Decision Brochure) will not be distributed as part of the packaged device. Rather, it will be bulk-shipped to the physician's office to be made available to patients. The patient labeling will also be posted on Mentor's website and will be sent to patients requesting it via their 800 phone number (1-800-MENTOR-8). If this product is approved, it will also be placed on FDA's website. The patient labeling is also the subject of the focus group study discussed in the **Mentor's Postapproval Plans** section above.

FDA requested Mentor to provide recommended wording for their labeling on several different topics. FDA acknowledges that some of the proposed wording will need to be modified to accurately reflect data/information from Mentor's PMA, the literature, or other sources, should the product be approved. Below are only those topics for which FDA is seeking Panel input as outlined in the Panel questions provided in Tab 2 of your Panel package. These labeling topics include: (1) the recommended method and frequency for screening for silent rupture; (2) recommendations for clinical management of suspicious and confirmed, intracapsular and extracapsular rupture; and (3) information on potential health consequences of extracapsular and migrated gel.

Below are the three labeling topics for which FDA will seek your input as to the extent to which Mentor's recommendations are supported by the available data/information. After each topic is FDA's discussion of that topic. Refer to Tab 3 of your Panel package for copies of Mentor's draft physician and patient labeling.

1. Method and Frequency for Screening for Silent Rupture

Proposed Package Insert Wording:

"PRECAUTIONS

5. Instructions to Patients:

- Follow-up Examinations- Patients should be instructed to have follow-up examinations on an annual or biannual basis, including assessment of implant integrity.

6. *Rupture*

- If there is a clinical suspicion of intracapsular or extracapsular rupture, consideration should be given to performance of a Magnetic Resonance Imaging (MRI) examination. If rupture is confirmed by any means, explantation is recommended."

Proposed Patient Brochure Wording:

"What are Precautions for You to Consider?

Further considerations:

• **Follow-up Examinations –** After breast implantation, it is recommended that you have follow-up examinations by your doctor on an annual or biannual basis.

• **Rupture –** If you suspect that your implant may be ruptured, you should consult your doctor. If rupture is confirmed by your doctor, it is recommended that you have your implant removed. You should monitor your breast implants for rupture when you check your breasts for lumps monthly. Examine your breast tissue by feeling for lumps. Then feel the breast implants. Move the implants around while looking in the mirror. Look for changes in shape, size and feel of the implants. Know, and pay attention to, how the breast implants feel on the inside and well as the outside. If you notice any changes, see your plastic surgeon so that he or she can examine the implants for rupture or other changes."

Mentor did not provide a specific recommendation regarding MRI screening. The Core Study demonstrated that most ruptures are not symptomatic; therefore, it is unclear to what extent either a physician or a patient will be able to detect a rupture by following the above instructions.

2. Clinical Management of Suspicious and Confirmed, Intracapsular and Extracapsular Rupture

Proposed Package Insert Wording:

"PRECAUTIONS

6. *Rupture*

- If there is a clinical suspicion of intracapsular or extracapsular rupture, consideration should be given to performance of a Magnetic Resonance Imaging (MRI) examination. If rupture is confirmed by any means, explantation is recommended."

Proposed Patient Brochure Wording:

"What are Precautions for You to Consider?

Further considerations:

• **Follow-up Examinations –** After breast implantation, it is recommended that you have follow-up examinations by your doctor on an annual or biannual basis.

• **Rupture –** If you suspect that your implant may be ruptured, you should consult your doctor. If rupture is confirmed by your doctor, it is recommended that you have your implant removed. You should monitor your breast implants for rupture when you check your breasts for lumps monthly. Examine your breast tissue by feeling for lumps. Then feel the breast implants. Move the implants around while looking in the mirror. Look for changes in shape, size and feel of the implants. Know, and pay attention to, how the breast implants feel on the inside and well as the outside. If you notice any changes, see your plastic surgeon so that he or she can examine the implants for rupture or other changes."

"What Are Potential Breast Implant Complications?
Ruptured implants require additional surgery to remove and to possibly replace the implant. Magnetic resonance imaging with equipment specifically designed for imaging the breast may be used for evaluating patients with suspected rupture or leakage of their silicone gel-filled breast implant.

Silicone gel, which escapes the scar tissue capsule surrounding the implant, may migrate away from the breast. The free silicone may cause lumps to form in the breast or other tissues (such as the chest wall, armpit, arm or abdomen). Plastic surgeons usually recommend removal of the implant if it has ruptured, even if the silicone is still enclosed with the capsule, because the silicone gel may eventually leak into surrounding tissues. If you are considering removal of an implant and the implantation of another one, be sure to discuss the benefits and risks with your doctor."

Mentor recommends removal of ruptured devices. This is consistent with clinical practice in the U.S., which is to remove implants that are confirmed to be ruptured. The last sentence in the patient labeling, however, implies that removal of ruptured implants is optional rather than recommended.

3. Potential Health Consequences of Extracapsular and Migrated Gel

Proposed Package Insert Wording:

"POTENTIAL ADVERSE EVENTS

• Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. A review of recent long term epidemiological studies of women with and without implants, together with the review of a number of previously conducted epidemiological studies, indicates that these diseases are no more common in women with implants than those in women without implants."

Proposed Patient Brochure Wording:

"2.0 What Are Potential Breast Implant Complications?

• Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases and symptoms, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature of small numbers of women with implants. A review of recent long-term epidemiological studies of women with and

> without implants,[67] together with the review of a number of previously conducted epidemiological studies,[68] indicates that these diseases and symptoms are no more common in women with implants than those in women without implants. However, a lot of women with breast implants believe that their implants caused a connective tissue disease."

Mentor focused their discussion on CTD. FDA believes that breast implant labeling should include a discussion of current literature on other topics.

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