SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Silicone Gel-Filled Breast Implants
Device Trade Name:	Mentor MemoryGel™ Silicone Gel-Filled Breast Implants
Applicant's Name and Address:	Mentor Corporation 201 Mentor Drive Santa Barbara, California 93111
Premarket Approval Application (PMA) Number:	P030053
Date of Panel Recommendation:	April 13, 2005
Date of Notice of Approval to Applicant:	November 17, 2006

II. INDICATIONS FOR USE

The Mentor MemoryGel Silicone Gel -Filled Breast Implant are indicated for females for the following uses (procedures):

- **Breast augmentation for women at least 22 years old.** Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of a primary breast augmentation surgery.

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

III. CONTRAINDICATIONS

Breast implant surgery should not be performed in:

- Women with active infection anywhere in their body.
- Women with existing cancer or pre-cancer of their breast who have not received adequate treatment for those conditions.
- Women who are currently pregnant or nursing.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Mentor MemoryGel Silicone Gel-Filled Breast Implants physician labeling.

V. DEVICE DESCRIPTION

Each Mentor MemoryGel Silicone Gel -Filled Breast Implant consists of a single-lumen, round silicone elastomer shell, with a patch on the posterior side, which is filled with MemoryGel, Mentor's proprietary silicone gel. The implants are available in a range of diameters, profiles (projections), and sizes, as well as in smooth and textured (Siltex) shell surfaces. The implants are provided dry-heat sterilized with a 5-year shelf life from the date of sterilization. Table 1 below shows the Mentor styles that are approved. Table 2 shows the general device materials for the shell, patch, and gel components.

Table 1: Approved Mentor MemoryGel Silicone Gel-Filled Breast Implants

Catalog Number	Description	Size Range
350-7100BC/7800BC	Smooth, Round, Moderate Profile	100-800cc
354-1007/8007	Textured, Round, Moderate Profile	100-800cc
350-1001BC/8001BC	Smooth, Round, Moderate Plus Profile	100-800cc
354-1001/8001	Textured, Round, Moderate Plus Profile	100-800cc
350-1254BC/8004BC	Smooth, Round, High Profile	125-800cc
354-4125/4800	Textured, Round, High Profile	125-800cc

Table 2: Device Materials

Component	Raw Material
Shell, inner/outer layers	Dimethyl Silicone Elastomer Dispersion
Shell, barrier layer	Diphenyl Silicone Elastomer Dispersion
Shell textured layer	MED 4750 Silicone Elastomer
Patch assembly	MED 4750 Silicone Elastomer
Gel	Silicone Gel: Base and Crosslinker; platinum cure

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative treatments include, but are not limited to, saline-filled breast implants, external prostheses, autogenous tissue grafts; tissue flaps (e.g., transverse rectus abdominis muscle, latissimus dorsi muscle, gluteal muscle), or no treatment.

VII. REGULATORY AND MARKETING HISTORY

Silicone gel-filled breast implants are preamendments devices. Mentor began marketing silicone gel-filled breast implants in the U.S. in 1984. In April 1991, FDA published a final 515(b) regulation calling for silicone gel-filled breast implant PMAs within 90 days (56 FR 14620). In April 1992, FDA determined that there were insufficient data to approve any of the PMAs submitted, and, therefore, Mentor's silicone gel breast implants were no longer marketed in the U.S. However, the FDA also determined that access to silicone gel-filled breast implants for reconstruction and revision patients should continue through adjunct clinical studies.

The Mentor Adjunct Study, which was started in 1992, was designed to address the public health need of reconstruction and revision patients. Local complications and satisfaction data were collected at 1, 3, and 5-year timepoints. However, with the approval of the subject PMA P030053, the public health need no longer exists and, while patient follow-up

continues through 5 years for those Adjunct Study patients currently enrolled, no new patients will be enrolled into the Mentor Adjunct Study.

In August 2000, Mentor received FDA approval and began their Core Study for their silicone gel-filled breast implant product. The Core Study is the primary clinical data set in this PMA.

Outside of the U.S., over 750,000 MemoryGel implants have been distributed worldwide from 1992 through 2005. The Mentor MemoryGel implants have not been withdrawn from any foreign market for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Based on those reported in literature and/or the Mentor Core Study, potential adverse events that may occur with breast implant surgery include reoperation (additional surgeries), implant removal with or without replacement, implant rupture, capsular contracture, wrinkling, asymmetry, implant displacement, implant palpability/visibility, scarring, ptosis, pain, changes in nipple and breast sensation, infection (including Toxic Shock Syndrome), hematoma, seroma, breast feeding difficulties, calcium deposits, extrusion, necrosis, delayed wound healing, breast tissue atrophy/chest wall deformity, and lymphadenopathy.

There have also been reports in the literature of other conditions in women with silicone gel-filled breast implants, including connective tissue disease (CTD), CTD signs and symptoms, neurological disease, neurological signs and symptoms, cancer, suicide, and potential effects on offspring. Many of these conditions have been studied to evaluate their potential association with breast implants, but no cause and effect relationship has been established between breast implants and these conditions.

Refer to Section X below for a summary of the adverse event data from the Mentor Core Study.

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies are divided into five sections: chemistry; toxicology; mechanical; modes and causes of rupture; and shelf life.

A. Chemistry Data

Chemical testing was performed on the major components (shell and gel) of Mentor's product to address the biological safety of the materials used in the Mentor product.

1. Extent of Crosslinking

Shell - Three Siltex Round Moderate Profile Gel-Filled (100 cc) devices were subjected to an additional thermal cure step consisting of 240 minutes at 164°C. The device shells were then subjected to exhaustive extraction conditions (M/V 1/200) before and after the additional thermal cure step. The crosslink chain density ($\rho_c N_{AV}$) was calculated to be 7.9×10^{19} chains/cm^3 by the Sol Fraction Method (equilibrium swell ratio). The three devices tested showed similar results, indicating that 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. The crosslink chain density ($\rho_c N_{AV}$) was calculated to be 1.46×10^{17} chains/cm^3. 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). Shells from unfilled devices (not exposed to gel) and from filled devices (exposed to gel) were tested. The shells not exposed to gel contained <11.1 µg/g of volatiles, of which the notable compounds were isopropanol (<1 ppm), xylenes (<0.08 ppm), methoxytrimethylsilane (3 ppm), dodecane (3 ppm), and undecane (1.4 ppm). The shells exposed to gel contained <10.2 µg/g of volatiles.

Gel - The analysis on the gel was performed with the same equipment as for the shell component, using a small sample of gel. The gel filler contained <2.8 µg/g of volatiles. The notable compounds were D4 (0.5 ppm), D5 (1.6 ppm), and undecane (<0.3 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 Table 3 below.

Table 3. Volatile Results

Compound	Shell Not Exposed to Gel (ppm)	Shell Exposed to Gel (ppm)	Gel Filler (ppm)	Whole Device (ppm)
D3	ND	0.19	0.18	0.18
D4	<0.06	0.23	0.49	0.46
D5	0.28	0.79	1.60	1.47
Methoxytrimethylsilane	3.13	3.34	ND	0.43
Dimethoxydimethylsilane	ND	0.20	ND	0.03
Methoxytriethoxysilane	0.04	ND	ND	ND
Tetramethyldiethyldisiloxane	ND	ND	0.05	0.04
Acetone	1.02	1.38	ND	0.18
Isopropanol	<1.06	2.03	ND	0.26
2-Pentanone	0.05	ND	ND	ND
Methyl Butanoate	0.04	ND	0.09	0.01
Ethylbenzene	<0.01	ND	ND	ND
m- & p-xylene	0.06	ND	<0.09	0.08
4-Methyl-3-penten-2-one	0.07	0.08	ND	0.01
o-xylene	<0.02	ND	ND	ND
Alpha-Pinene	<0.02	ND	ND	ND
Cyclohexanone	<0.56	ND	ND	ND
1-Ethyl-2-methylbenzene	0.02	0.06	ND	0.01
Decane	0.09	ND	ND	ND
Benzaldehyde	0.04	0.08	ND	0.01

Compound	Shell Not Exposed to Gel (ppm)	Shell Exposed to Gel (ppm)	Gel Filler (ppm)	Whole Device (ppm)
1,3,5-Trimethylbenzene	0.04	0.04	ND	0.01
Limonene	0.02	0.05	ND	0.01
Undecane	1.39	<0.45	<0.34	0.35
Acetophenone	0.03	0.06	ND	0.01
Dodecane	3.00	<0.55	ND	0.07
Total Volatiles	<11.07	<10.16	<2.84	3.67

Data preceded with a "<" symbol means that the level of the individual component, if present, was below the method detection limit indicated.
ND=Not detected.

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 as described below.

Gravimetric Analysis - Shells not exposed to gel gave 1.86% by weight of extractable residue. Shells exposed to gel gave 10.43% by weight of extractable residue. The gel gave 82.74% by weight of extractable residue. The whole device gave 72.96% 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 phenyl groups were detected because of their low concentrations.

Gel Permeation Chromatography - With regard to the shell exposed to gel, the extractable residue on GPC analysis gave five peaks: (1) a larger molecular weight (M_w) peak at about 17,400 Daltons for polydimenthylsiloxane and (2) an additional four peaks of 770, 550, 260, and 170 Daltons. The larger molecular weight peak represented a methyl substituted polysiloxane polymer with a polydispersity of 1.8. Its origin was determined to be from the gel.

With regard to the shell not exposed to gel, the extractable residue contained phenyl polymer, oligomer and monomeric species with a molecular weight (M_w) range of 170 - 61,000 Daltons. The phenyl substituted siloxanes concentrations ranged from 32 to 620 ppm. The extract also yielded two peaks of dimethyl siloxane species, one with a molecular weight of 341,000 Daltons, and a second one with a molecular weight of 4,820 Daltons. The high molecular weight species represented less than 10% of the total peak area.

With regard to the gel, the extractable residue on GPC analysis gave only one peak with a polydispersity of 2.4 (M_w = 53,900 and M_n = 22,300; M_w / M_n = 2.4).

Semi-Volatile Qualitative and Quantitative Analyses - With regard 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 34 ppm of D5 – D10. It also contained a total of approximately 220 ppm of linear dimethyl siloxanes. The total amount of vinyl-modified cyclic siloxanes was <52 ppm, and the total amount of phenyl-modified cyclic siloxanes was <68 ppm.

With regard to the gel extractables, extraction residue from the filler on GC/MS analysis was shown to contain 0.5 ppm of D4 and approximately 3800 ppm of D4-D21. Linear dimethylsiloxanes were determined to be 377 ppm. Vinyl modified siloxanes were 123 ppm, while no phenyl-modified 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 Table 4 below.

Table 4. Semi-Volatile Data

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	ND	0.5	ND	0.5
D_5	ND	2.5	<2.5	<2.5
D_6	ND	4.9	<4.2	<4.8
D_7	ND	9.0	<4.2	<8.4
D_8	<7.8	8.5	<7.6	<8.4
D_9	<7.8	8.4	<7.6	<8.3
D_{10}	<7.8	11.5	<7.6	<10.92
D_{11}	<12.2	23.3	<12.9	<21.86
D_{12}	22.2	35.3	17.6	32.92
D_{13}	48.5	51.0	27.8	47.85
D_{14}	148.3	118.7	77.6	113.11
D_{15}	201.3	181.5	114.7	172.4
D_{16}	207.0	217.8	114.6	203.8
D_{17}	530.3	616.4	383.7	584.9
D_{18}	387.8	560.7	356.0	533.0
D_{19}	272.88	450.9	292.2	429.4
D_{20}	521.62	657.8	303.9	609.9
D_{21}	325.69	845.6	328.0	775.5
Linear Dimethyl Siloxanes				
MD_7M	ND	<1.5	ND	<1.3
MD_8M	ND	1.7	ND	1.5
MD_9M	ND	3.2	ND	2.8
$MD_{10}M$	ND	7.2	NA	6.2
$MD_{11}M$	ND	13.5	<11.2	<13.2
$MD_{12}M$	ND	37.2	20.1	34.8
$MD_{13}M$	ND	54.6	29.3	51.2
$MD_{14}M$	ND	66.1	40.2	62.6
$MD_{15}M$	ND	70.0	41.5	66.2
$MD_{16}M$	ND	57.2	40.0	54.9
$MD_{17}M$	ND	64.9	38.1	61.3

Compound	Shell Not Exposed to Gel (µg/g)	Gel Filler (µg/g)	Shell Exposed to Gel (µg/g)	Whole Device (µg/g)
Vinyl-Modified Cyclic Dimethylsiloxanes				
$D^{vi}D_{14}$	ND	6.8	ND	5.9
$D^{vi}D_{15}$	ND	10.1	NA	8.8
$D^{vi}D_{16}$	ND	14.0	<16.7	<14.4
$D^{vi}D_{17}$	ND	26.1	ND	22.6
$D^{vi}D_{18}$	ND	40.6	NA	35.1
$D^{vi}D_{19}$	ND	25.0	<35.1	<26.4
Phenyl-Modified Cyclic Dimethylsiloxanes				
$D_{10}D^{Ph}$	<8.9	ND	ND	ND
$D_{11}D^{Ph}$	<8.9	ND	ND	ND
$D_{12}D^{Ph}$	<8.9	ND	ND	ND
$D_2D^{Ph}{}_2$ (1)	48.4	ND	14.4	2.0
$D_2D^{Ph}{}_2$ (2)	37.1	ND	<9.9	<1.3
$D_3D^{Ph}{}_2$ (1)	58.9	21.9	<9.9	<20.2
$D_3D^{Ph}{}_2$ (2)	78.6	19.8	13.6	19.0
$D_4D^{Ph}{}_2$ (1)	21.4	ND	<9.9	<1.3
$D_4D^{Ph}{}_2$ (2)	23.1	ND	<9.9	<1.3
$D_5D^{Ph}{}_2$ (1)	<8.9	ND	ND	ND
$D_5D^{Ph}{}_2$ (3)	<8.9	ND	ND	ND
$D_5D^{Ph}{}_2$ (2)	<8.9	ND	ND	ND
Miscellaneous Siloxanes				
Siloxane	ND	4.2	1.8	3.9
Residues of Solvents and Plasticizers				
o-Xylene	ND	<0.4	ND	<0.4
Di(Ethylhexyl) Phthalate	<11.2	ND	ND	ND
Total (µg/g)	<3055.8	<4350.1	<2403.8	<4086.7

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

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

4. Heavy Metal Analysis

Both the shell and the gel components were extracted with aqueous (buffer) and organic solvents and analyzed by Inductively Coupled Plasma/Mass spectroscopy) (ICPM) for numerous metals. The metal concentrations obtained from the extracted residues are shown in Table 5 below for the device, as a whole.

Table 5: Heavy Metal Concentrations

Metal Name	Concentration (ppm)
Antimony	0.014
Arsenic	0.123
Barium	0.001
Beryllium	0.006
Cadmium	0.002
Chromium	0.028
Cobalt	0.052
Copper	0.025
Lead	0.011
Magnesium	0.391
Mercury	0.004
Molybdenum	0.001
Nickel	0.050
Platinum	0.299
Selenium	0.069
Silver	0.001
Tin	0.004
Titanium	0.033
Vanadium	0.310
Zinc	0.034

In addition, platinum metal analyses were conducted on the unextracted shell and the gel components. The platinum concentration was found to be 8.8 ppm for the unextracted shell and 4.8 ppm for the unextracted gel.

As a note, platinum is a metal used as a catalyst in the manufacture of the shell and gel components of silicone breast implants. The small amounts of platinum remaining in the product following manufacturing may enter the body, either by diffusing through the intact shell (i.e., through gel bleed) or through an implant rupture. Based on our review of the gel bleed testing, the published literature on this topic, as well as the biocompatibility testing and clinical data on the device, FDA concluded that the platinum contained in breast implants is in the zero oxidation state, which has the lowest toxicity and, thus, does not pose a significant risk to women with silicone breast implants.

FDA has posted a Backgrounder on its website, which provides a brief summary of some of the key scientific studies on platinum and silicone gel-filled breast implants (http://www.fda.gov/cdrh/breastimplants/).

5. Silica Filler

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

B. Toxicology Data

Mentor provided both pharmacokinetic and biocompatibility testing to address the biological safety of the materials used in the Mentor product.

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.[1] injected rats with 2ml of silicone gel at two 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.

With regard to the migration of the low molecular weight mixtures of cyclic siloxanes (e.g., D4, D5, D6), Kala, et al. [2] injected a concentrated 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 examined contained some cyclosiloxanes. The high dose used far exceeded the dose from implants. The survival of the mice for one year at these levels of cyclosiloxane exposure indicates a high level of safety.

Anderson, et al.[3] studied the distribution of D4 in rats using radiolabeled D4 administered by inhalation at 700 ppm. The radioactivity was widely distributed in rat tissues, but only 5-6% of the dose was retained in the tissues. Based on these results, the authors proposed that there is high pulmonary and hepatic clearance of D4. Another model of the same data predicted some accumulation in the fat depots.[4]

Biocompatibility Testing

The biocompatibility testing below was conducted on the major device components (shell, gel, and patch), as described in ISO 10993.[5] This testing demonstrated the biocompatibility of the materials in the Mentor implants.

1. Cytotoxicity

Cytotoxicity testing was conducted on the dimethyl and diphenyl elastomer dispersions, the MED 4750 elastomer, the silicone gel, and the dispersion coating. In addition, a complete (100 ml) gel device was tested. The studies used mouse fibroblast L929 cells. Most materials were tested by both the agarose overlay method in which the device or material is placed directly on an agar overlay of the cells, and by the USP elution method, in which the device or material 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 results showed that the test articles were non-cytotoxic.

2. Short Term Irritation and Implantation

The test articles tested for irritation and/or implantation included the dimethyl and diphenyl elastomer dispersions, the MED 4750 elastomer, the silicone gel, the dispersion coating, and

the laser-marked patches. 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 to any of these materials.

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 laser-marked 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.

The studied showed that none of the device materials causes significant irritation.

3. Acute Systemic Toxicity

The test articles evaluated for acute systemic toxicity included the dimethyl and diphenyl elastomer dispersions, the MED 4750 elastomer, silicone gel, dispersion coating, a textured gel-filled device, a smooth device, and laser-marked patches. Extracts for testing were prepared by using 60cm^2 per 20ml of solvent of each device components for extraction into saline and cottonseed oil. The saline extracts were injected into mice intravenously at 50 ml/kg, and the oil extracts were injected intraperitoneally at the same dose. The animals were observed for toxic signs. No toxicity was observed.

4. Hemocompatibility

Hemocompatibility testing was conducted by measuring the extent of red cell lysis produced by direct contact with, and/or extracts of, the following device components: dimethyl and diphenyl elastomer dispersions, the MED 4750 elastomer, and silicone gel. 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. No significant hemolysis was seen with any of these device components.

5. Pyrogenicity

Rabbit pyrogen studies using a complete textured device 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 device 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 device was tested in the same way. The results showed that the test articles were non-pyrogenic.

6. Immunotoxicity

Immunotoxicity tests were conducted by implanting disks punched from smooth or textured shells 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 for 28 days.

In tests involving the smooth shells, 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 shell and patch. An additional test 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 that also bind the Thy 1.2^+ antibody. Thus, there were no immunological abnormalities in the first experiment.

In a second test, the smooth shell was implanted in mice for 10 days. 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. This testing, combined with the first set of testing, showed that the smooth shell did not alter the immune response.

In another set of experiments, the textured shell was tested. The protocols are very similar to the smooth shell 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 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.

7. Sensitization

Sensitization testing was performed on the dimethyl and diphenyl elastomer dispersions, the MED-4750 elastomer, the dispersion coating, and the laser engraved patches. Variations of the Guinea Pig Maximization test method were used. CSO and saline extracts of device components were injected intradermally, and, a week later, petrolatum with sodium laurel sulfate (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.

8. Reproductive Toxicity and Teratogenicity

Mentor conducted a two-generation study in rats to assess the teratogenic and reproductive toxicity potential of Mentor's shell. In order to exaggerate the dose of potentially extractable materials, the elastomeric test material was pulverized prior to implantation, thus significantly increasing the exposed surface area. The findings of this study indicated that, compared to the controls, pulverized patched and/or valved silicone elastomer shells did not cause reproductive or teratogenic effects when implanted subcutaneously in female rats in two consecutive generations. Mentor also has conducted an extended one-generation study of Mentor silicone gel administered by subcutaneous injection in rats. There were no effects on maternal growth, estrous cycling, fertility, fecundity, pregnancy, delivery, or lactation. In addition, there were no effects on F1 offspring survival, growth, acquisition of developmental landmarks, learning and memory, functional observational battery, hormone-mediated endpoints, systemic or reproductive organ weights, or organ histopathology.

9. Genotoxicity

Mentor addressed genotoxicity testing 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 Test (*Salmonella* Assay) was used to test the dimethyl and diphenyl elastomer dispersions, the MED 4750 elastomer, the dispersion coat, shell, and extracts of the complete implant. There were no significant genotoxic effects.

In a second set of data, Mentor used unscheduled DNA synthesis to test a 275ml smooth device. 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.

In a third set of data, Chromosome Aberration Assays were conducted in CHO Cells. Saline and alcohol extracts of a 275ml smooth device 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.

A fourth set of data were obtained using an in-vivo mouse micronucleus test. The test article was a 300ml textured device. The device was cut into small pieces through all layers and extracted into saline and corn oil at a ratio of 1g of device per 5ml 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.

10. Carcinogenicity

Because of the negative mutagenicity testing and a negative mouse micronucleus test, additional carcinogenicity testing was not requested by FDA. Nevertheless, Mentor provided some carcinogenicity tests that were performed using a silicone gel manufactured by Dow Corning that is equivalent to the gel used in the Mentor product.

In the first set of data, Mentor performed carcinogenicity testing in albino rats using various silicone gels manufactured by Dow Corning. 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 of 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.

In the second set of data, Mentor performed 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. It is unlikely that the silicone gel contains 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 by the device implants.

C. Mechanical Data

This section includes a summary of the fatigue, gel bleed, and gel cohesion testing that Mentor provided in support of establishing the safety of their product.

1. Fatigue Testing

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. The test set-up consisted of a uniaxial test fixture of parallel plates in a test chamber containing circulating physiologic saline solution at 37°C. The applied cyclic loads ranged from 20-100 lbs. Testing was performed at 1 Hz for all higher loads and at 5 Hz for the lower loads, which was justified by comparative fatigue testing at 1 Hz and 5 Hz for 40 and 80 lbs. A minimum of three implants for each style was tested for most load levels. Runout was defined as 10 million cycles. The resulting endurance load levels were 20-30 lbs. As expected, based on the test set-up, all fatigue failure modes were radial tears. FDA believes that these data demonstrated that the Mentor product can withstand large static loading and in-vivo cyclic loading. See Section XI below for more details.

2. Gel Bleed Testing

Mentor provided testing 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. Mentor's test method, which was designed to mimic in-vivo exposure to silicone gel-filled breast implants, involved the incubation of smooth implants in porcine serum at 37°C. At specific timepoints, samples of the solution were withdrawn for analysis for low molecular weight (LMW) silicones and platinum. The results indicated that the diffusion of measured constituents ceased by 60 days and that only the LMW silicones D4, D5, and D6, and platinum, bled into the serum in measurable quantities. In total, 4.7µg of these three LMW silicones was detected. Platinum levels measured at 4.1µg by 60 days, by which time an equilibrium level was reached and no more platinum diffused through the device shell. Over 99% of the LMW silicones and platinum stayed in the implant.

With regard to the health consequences of gel bleed, the literature has reported small quantities of LMW silicone compounds, as well as platinum (in zero oxidation state), have been found to diffuse ("bleed") through an intact implant shell.[6,7] The evidence is mixed as to whether there are any clinical consequences associated with gel bleed. For instance, studies on implants implanted for a long duration have suggested that such bleed may be a contributing factor in the development of capsular contracture and lymphadenopathy.[8] However, evidence against gel bleed being a significant contributing factor to capsular contracture and other local complications is provided by the fact that there are similar or lower complication rates for silicone gel-filled breast implants than for saline-filled breast implants. Saline-filled breast implants do not contain silicone gel and, therefore, gel bleed is not an issue for those products. Furthermore, toxicology testing has indicated that the silicone material used in the Mentor implants does not cause toxic reactions in test animals. It should also be noted that studies reported in the literature have demonstrated that the low concentration of platinum contained in breast implants is in the zero oxidation (most biocompatible) state.[9,10,11,12] The literature finding has been confirmed by two separate studies sponsored by Mentor. The overall body of available evidence supports that the extremely low level of gel bleed for Mentor's product is of no clinical consequence.

3. Gel Cohesion Testing

Gel cohesivity and penetration testing assess the cohesive and cure characteristics of silicone gel, respectively. Gel cohesivity testing was performed as per ASTM F703 (cone/pendant method) using gel from final finished product. The majority of the 100 samples showed no measurable pendant length, while a few samples showed an average pendant length of 0.1cm, which meets the ASTM F703 specification of <4.5cm. Gel penetration testing was performed as per a Mentor test method involving measurement of the penetration of a plunger into in-process gel in a jar. All samples passed Mentor's internal penetration specification.

D. Modes and Causes of Rupture

Mentor provided numerous test reports and other information to characterize modes and causes of failure of their device for a range of in-vivo times, such as failure analyses of retrieved devices (i.e., retrieval study), physical property testing, assessment of manufacturing processes and surgical techniques that may impact rupture, and a review of the explant literature.

The primary set of modes and causes of rupture data was a retrieval study that involved 274 explanted, single-lumen Adjunct and Core Study devices that were determined to have failed upon laboratory observation (intact devices were excluded from this dataset). The samples analyzed were explanted anywhere from time 0 (damaged during the implantation procedure and, thus, not implanted) up to 10 years after implantation. For these 274 explants, the failure modes were surgical instrument damage (n=119); localized shell stress from the implantation procedure (n=98); fold flaw (n=20); opening at the shell/patch junction (n=23); shell/patch delamination (n=11); and opening within the patch (n=3). FDA determined that these data are adequate to characterize the modes and causes of rupture through approximately 10 years. See Section XI below for more details.

D. Shelf Life Data

Mentor's shelf life testing was performed on both the smooth and textured devices (gel cohesion, tension set, shell/patch joint strength, ultimate elongation, and break force) and the package (thermoform dye penetration and peel seal strength). Real-time testing was the primary set of data used to establish the shelf life of the Mentor product. All device and package testing met the acceptance criteria set in the protocol. Accordingly, the data supported a 5-year shelf life for the Mentor product.

X. SUMMARY OF THE MENTOR CORE STUDY

The Mentor Core Study is the primary set of clinical data. These data are summarized below.

A. Study Design

The Mentor Core Study is a 10-year study to assess safety and effectiveness in 1,007 augmentation, reconstruction, and revision (revision-augmentation and revision-reconstruction) patients. Patient medical histories and baseline clinical data were collected preoperatively. Patient follow-up is at 6 months, 1 year, 2 years, and annually through 10 years. Rupture is assessed for patients who have scheduled MRIs at years 1, 2, 4, 6, 8, and 10 years to screen for silent rupture (i.e., MRI cohort) and those who are not assessed for rupture by scheduled MRIs (i.e., non-MRI cohort).

Safety assessments include complication rates, reasons for reoperation, and reasons for implant removal. Effectiveness assessments include circumferential chest size change and bra cup size change (typically only augmentation patients), patient satisfaction, and quality of life (QoL). QoL is comprised of measures of self-esteem, body image, and general health outcome. The results through 3 years are currently being reported, and the study remains ongoing. Mentor will periodically update labeling as more information becomes available.

B. Patient Accounting and Baseline Demographic Profile

The Mentor Core Study consists of 1,007 patients, including 551 primary augmentation patients, 146 revision-augmentation patients, 251 primary reconstruction patients, and 59 revision-reconstruction patients. Three-year data are available for 88% of the eligible primary augmentation patients, 87% of the eligible revision-augmentation patients, 82% of the eligible primary reconstruction patients, and 86% of the revision-reconstruction patients.

Demographic information for the Core Study with regard to race is as follows: 90% of the Core Study patients were Caucasian; 2% were Asian; 2% were African American; and 6% were other. The mean age at surgery was 34 years for primary augmentation patients, 42 for revision-augmentation patients, 45 years for primary reconstruction patients, and 51 years for revision-reconstruction patients. Approximately 61% of the Core Study patients were married. Approximately 82% had some college education.

With respect to surgical baseline factors, for primary augmentation patients, the most frequently used devices were smooth implants (70%), the most common incision site was inframammary (59%), and the most frequent site of placement was submuscular (66%). For

revision-augmentation patients, the most frequently used devices were smooth implants (68%), the most common incision site was inframammary (71%), and the most frequent site of placement was submuscular (63%). For primary reconstruction patients, the most frequently used devices were textured implants (58%), the most common incision site was the mastectomy scar (56%), and the most frequent site of placement was submuscular (87%). For revision-reconstruction patients, the most frequently used devices were smooth implants (63%), the most common incision site was mastectomy scar (50%), and the most frequent site of placement was submuscular (83%).

C. Complication Rates

Table 6 below shows the 3-year, by-patient, cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of complications.

Table 6: KM Risk Rates through 3 Years

KM Rates through 3 Years[1]		Primary Augmentation[2] N=551	Revision-Augmentation[3] N=146	Primary Reconstruction[4] N=251	Revision-Reconstruction[5] N=59
Any complication (including reoperation)		36.6% (32.1, 40.2)	50.1% (41.9, 58.3)	49.4% (42.9, 55.8)	47.5% (34.8, 60.3)
Any reoperation		15.4% (12.3, 18.4)	28.0% (20.4, 35.6)	27.0% (21.4, 32.6)	29.1% (17.4, 40.7)
Implant removal with or without replacement		4.9% (3.1, 6.7)	13.4% (7.5, 19.3)	12.7% (8.5, 16.9)	13.7% (4.9, 22.6)
Asymmetry		0.5% (0.0, 1.2)	0	6.7% (3.4, 10.0)	8.9% (1.4, 16.3)
Breast mass		3.1% (1.6, 4.6)	6.6% (2.4, 10.7)	3.6% (1.1, 6.0)	7.0% (0.4, 13.7)
Breast pain		1.7% (0.6, 2.8)	1.5% (0.0, 3.4)	2.2% (0.3, 4.2)	3.5% (0.0, 8.2)
Breast sensation changes		2.2% (1.0, 3.4)	2.1% (0.0, 4.5)	1.0% (0.0, 2.5)	1.9% (0.0, 5.7)
Capsular contracture III/IV		8.1% (5.8, 10.4)	18.9% (12.5, 25.4)	8.3% (4.7, 11.9)	16.3% (5.0, 27.6)
Delayed wound healing		0	2.1% (0.0, 4.4)	0.4% (0.0, 1.2)	1.7% (0.0, 5.0)
Granuloma		0.2% (0.0, 0.5)	0.8% (0.0, 2.5)	0	5.1% (0.0, 10.7)
Hematoma		2.6% (1.2, 3.9)	2.8% (0.09, 5.4)	1.3% (0.0, 2.8)	3.5% (0.0, 8.2)
Implant extrusion		0	1.4% (0.0, 3.3)	1.2% (0.0, 2.6)	1.7% (0.0, 5.0)
Implant malposition/ displacement		0.4% (0.0, 0.9)	1.4% (0.0, 3.3)	1.7% (0.05, 3.3)	8.5% (1.4, 15.7)
Implant palpability/visibility		0	0.7% (0.0, 2.1)	0	0
Implant rupture	MRI cohort	0.5% (0.0, 1.6)	7.7% (0.4, 15.0)	0.9% (0.0, 2.5)	0
	Non-MRI cohort	0	0	0	0
Infection		1.5% (0.5, 2.5)	1.4% (0.0, 3.4)	5.7% (2.8, 8.6)	0
Inflammation		0.7% (0.02, 1.4)	1.4% (0.0, 3.3)	0	1.7% (0.0, 5.1)
Lactation difficulties		0.2% (0.0, 0.6)	0.8% (0.0, 2.2)	0	0
Lymphadenopathy		0	0	0.9% (0.0, 2.6)	0
Metastatic disease		0	0	1.8% (0.05, 3.6)	0
Miscarriage		1.5% (0.5, 2.6)	0.9% (0.0, 2.5)	0.9% (0.0, 2.0)	0
Necrosis		0.2% (0.0, 0.6)	0	0.9% (0.0, 2.3)	0
New diagnosis of breast cancer		0	0	0.5% (0.0, 1.4)	1.7% (0.0, 5.1)
New diagnosis of rheumatic disease		0.6% (0.0, 1.2)	0.8% (0.0, 2.5)	0.4% (0.0, 1.3)	3.5% (0.0, 8.1)
Nipple complications		10.4% (7.8, 12.9)	10.5% (5.5, 15.5)	3.3% (0.8, 5.7)	1.7% (0.0, 5.0)
Ptosis		2.3% (1.0, 3.6)	1.5% (0.0, 3.6)	6.9% (2.7, 11.2)	3.4% (0.0, 8.0)
Rash		0.7% (0.02, 1.4)	0	1.0% (0.0, 2.3)	0
Recurrent breast disease		0	0	1.7% (0.05, 3.4)	1.7% (0.0, 5.0)
Scarring/Hypertrophic Scarring		6.7% (4.6, 8.8)	8.4% (3.9, 13.0)	6.8% (3.6, 10.0)	3.6% (0.0, 8.4)
Seroma		0.9% (0.1, 1.7)	2.1% (0.0, 4.4)	4.9% (2.2, 7.5)	1.7% (0.0, 5.0)
Trauma		1.3% (0.2, 2.3)	0.9% (0.0, 2.5)	0.4% (0.0, 1.2)	1.7% (0.0, 5.0)
Wrinkling		0.7% (0.02, 1.5)	2.1% (0.0 4.5)	2.6% (0.5, 4.6)	7.0% (0.4, 13.6)

KM Rates through 3 Years[1]	Primary Augmentation[2] N=551	Revision-Augmentation[3] N=146	Primary Reconstruction[4] N=251	Revision-Reconstruction[5] N=59
Deep vein thrombosis	0.2% (0.0, 0.6)	0	0.4% (0.0, 1.2)	0
Muscle spasm	0	0.7% (0.0, 2.1)	0.4% (0.0, 1.2)	0
Placement damage	0.7% (0.02, 1.4)[6]	0	0	0
Anaphlyaxis	0.2% (0.0, 0.6)	0	0	0
Biopsy pending	0.2% (0.0, 0.6)	0	0	0
Bruising	0.4% (0.0, 0.9)	0	0	0
Position dissatisfaction	0.2% (0.0, 0.5)	0	0	0
Positive antinuclear antibodies for lupus	0.3% (0.0., 0.9)	0	0	0
Suture reaction	0.5% (0.0, 1.2)	0	0	0
Stitch abscess	0	0	0.6% (0.0, 1.6)	0
Tight benilli suture	0	0	0.4% (0.0, 1.3)	0
Redness	0	0	0.6% (0.0, 1.6)	0
Back/neck pain related to large implants	0	0.7% (0.0, 2.1)	0	0
Ectopic pregnancy	0	0.7% (0.0, 2.2)	0	0
False positive for rupture on mammogram	0	0.8% (0.0, 2.5)	0	0
Capsular tear with no pain or implant malposition	0	0	0	1.7% (0.0, 5.0)
Numbness in both hands at night	0	0	0	1.8% (0.0, 5.3)

[1] Excludes mild occurrences of asymmetry, breast pain, calcification, implant malposition/displacement, nipple sensation changes, breast sensation changes, nipple complications, and wrinkling. Also excludes planned second stage surgeries.
[2] 197 primary augmentation patients experienced at least one complication or reoperation.
[3] 119 primary reconstruction patients experienced at least one complication or reoperation.
[4] 72 revision-augmentation patients experienced at least one complication or reoperation
[5] 28 revision-reconstruction patients experienced at least one complication or reoperation.
[6] Breast implants were damaged during insertion and removed while the patient was still on the operating table.

D. Main Reasons for Reoperation

Table 7 below shows the main reasons for reoperations, stratified by indication, through 3 years. The rates are based on the total number of reoperations for that indication.

Table 7: Main Reasons for Reoperations through 3 Years

Reasons for Reoperation through 3 Years[1]	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
	N=109 Reops in 83 Patients	N=58 Reops in 39 Patients	N=79 Reops in 66 Patients	N=24 Reops in 17 Patients
Asymmetry	5 (4.6%)	1 (1.7%)	16 (20.3%)	1 (4.2%)
Biopsy	6 (5.5%)	6 (10.3%)	11 (13.9%)	7 (29.2%)
Breast cancer	0	0	3 (3.8%)	1 (4.2%)
Breast pain	1 (0.9%)	0	1 (1.3%)	0
Capsular contracture II	7 (6.4%)	5 (8.6%)	2 (2.5%)	0
Capsular contracture III/IV	33 (30.3%)	18 (31.0%)	8 (10.1%)	3 (12.5%)
Capsule/pocket tear	1 (0.9%)	0	0	1 (4.2%)
Delayed wound healing	2 (1.8%)	5 (8.6%)	1 (1.3%)	0
Follicular cyst/palpable nodule	0	0	0	2 (8.3%)
Hematoma/seroma	12 (11.0%)	5 (8.6%)	3 (3.8%)	1 (4.2%)
Implant extrusion	1 (0.9%)	2 (3.4%)	2 (2.5%)	1 (4.2%)
Implant malposition	2 (1.8%)	2 (3.4%)	9 (11.4%)	2 (8.3%)
Implant palpability/visibility	0	0	1 (1.3%)	0
Implant rupture (suspected)[2]	1 (0.9%)	1 (1.7%)	0	1 (4.2%)
Infection	3 (2.8%)	1 (1.7%)	4 (5.1%)	0
Muscle spasm	0	0	1 (1.3%)	0
Necrosis	1 (0.9%)	0	0	0
Nipple complications (unplanned)	0	0	2 (2.5%)	1 (4.2%)
Patient request for style/size change	16 (14.7%)	7 (12.1%)	9 (11.4%)	1 (4.2%)
Ptosis	4 (3.7%)	1 (1.7%)	3 (3.8%)	1 (4.2%)
Scarring/hypertrophic scarring	12 (11.0%)	3 (5.2%)	3 (3.8%)	0
Wrinkling	2 (1.8%)	1 (1.7%)	0	1 (4.2%)

[1]The reoperation rate excludes planned secondary surgeries. If more than one reason for a given reoperation was reported, the following hierarchy was used to determine a primary reason for that reoperation: rupture/deflation; infection; capsular contracture; necrosis/extrusion; hematoma/seroma; delayed wound healing; breast pain; implant malposition; wrinkling; palpability/visibility; asymmetry; ptosis; scarring; nipple complications; device injury/iatrogenic; breast cancer mass; biopsy; and patient request for style/size change.

[2]The implant was removed and found to be intact.

E. Main Reasons for Implant Removal

Table 8 below shows the main reasons for removal, stratified by indication, through 3 years. The rates are based on the total number of explantations for that indication.

Table 8: Main Reasons for Implant Removal through 3 Years

Reasons for Implant Removal through 3 Years	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
	N=45 Explants in 26 Patients	N=30 Explants in 18 Patients	N=41 Explants in 31 Patients	N=11 Explants in 8 Patients
Abnormal mammogram	0	1 (3.3%)	0	0
Asymmetry	0	1 (3.3%)	10 (24.4%)	2 (18.2%)
Breast pain	2 (4.4%)	0	0	0
Capsular contracture II	0	0	1 (2.4%)	0
Capsular contracture III/IV	5 (11.1%)	10 (33.3%)	4 (9.8%)	3 (27.3%)
Contralateral explantation	1 (2.2%)	0	0	0
Hematoma	0	0	1 (2.4%)	0
Implant extrusion	0	1 (3.3%)	2 (4.9%)	1 (9.1%)
Implant malposition	0	0	3 (7.3%)	0
Implant rupture (suspected)	1 (2.2%)[1]	1 (3.3%)[1]	0	0
Infection	2 (4.4%)	1 (3.3%)	2 (4.9%)	0
Lack of projection	0	0	1 (2.4%)	0
Muscle spasm	0	0	1 (2.4%)	0
Necrosis	2 (4.4%)	0	0	0
Patient request for style/size change	31 (68.9%)	14 (46.7%)	15 (36.6%)	2 (18.2%)
Pocket tear	0	0	0	1 (9.1%)
Recurrent breast cancer	0	0	1 (2.4%)	0
Scarring/hypertrophic scarring	0	1 (3.3%)	0	0
Symmastia	0	0	0	2 (18.2%)
Wrinkling	1 (2.2%)	0	0	0

[1]The implant was removed and found to be intact.

F. Other Clinical Safety Outcomes

Below is a summary of clinical findings from the Mentor Core Study with regard to connective tissue disease (CTD), CTD signs and symptoms, cancer, lactation complications, reproduction complications, and suicide. These issues, along with others, will be further evaluated beyond 3 years as part of a Mentor postapproval study of a large number of patients followed through 10 years.

CTD Diagnoses

Three primary augmentation patients and one revision-augmentation patient in the Mentor Core Study were reported to have a new diagnosis of CTD according to a rheumatologist. These diagnoses were Hashimoto's Thyroiditis at 2 years, two cases of rheumatoid arthritis at 2 and 3 years, and hypothyroidism at 2 years. One primary reconstruction patient and two revision-reconstruction patients in the Mentor Core Study were reported to have a new diagnosis of CTD according to a rheumatologist. These diagnoses were two cases of fibromyalgia, both at 1 year, and pyoderma gangrenosum at 1 year. It cannot be concluded that these CTD diagnoses were or were not caused by the implants because there was no comparison group of similar women without implants.

CTD Signs and Symptoms

Data on over 100 self-reported signs and symptoms, including about 50 self-reported rheumatological symptoms, were collected. Compared to before having the implants, statistically significant increases were found for fatigue, exhaustion, joint swelling, joint pain, numbness of hands, frequent muscle cramps, and the combined categories of fatigue, pain, and fibromyalgia-like symptoms in primary augmentation patients and for joint pain in revision-augmentation and primary reconstruction patients. These increases were not found to be related to simply getting older over time. No statistically significant increases were found for any individual signs and symptoms in the revision-reconstruction patients.

The Mentor Core Study was not designed to evaluate cause and effect associations because there is no comparison group of women without implants, and because other contributing factors, such as medications and lifestyle/exercise, were not studied. Therefore, it cannot be determined whether the increases were due to the implants or not, based on the Core Study. However, patients should be aware that they may experience an increase in these symptoms after receiving breast implants.

Cancer

There were no primary augmentation patients with new diagnoses of breast cancer through 3 years in the Mentor Core Study. As previous breast cancer was an exclusion criteria for primary augmentation patients, there were no reports of breast cancer reoccurrence in this indication. There were no reports of new diagnoses or reoccurrence in revision-augmentation patients. For primary reconstruction patients, 1 (0.5%) patient had a new diagnosis of breast cancer and 4 (1.7%) patients had a reoccurrence of breast cancer. For revision-reconstruction, 1 (1.7%) patient had a new diagnosis of breast cancer and 1 (1.7%) patient had a recurrence of breast cancer. There were no reports of other cancers, such as brain, respiratory, or cervical/vulvar, in any indication.

Lactation Complications

Two (8%) of the 25 primary augmentation patients who attempted to breast feed following breast implantation in the Mentor Core Study through 3 years experienced difficulty with breast feeding. For the 7 revision-augmentation patients who attempted to breast feed, 1 (14%) had difficulty breast feeding. For primary reconstruction patients, of the 3 women who attempted to breastfeed, none experienced lactation difficulties. None of the revision-reconstruction patients attempted to breast feed.

Reproduction Complications

Eight (1.5%) of the primary augmentation patients in the Mentor Core Study reported a miscarriage through 3 years. For primary reconstruction patients, 2 (0.9%) patients reported a miscarriage. There were no reports of miscarriage in revision-augmentation or revision-reconstruction patients.

Suicide

There were no reports of suicide in the primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction indications in the Mentor Core Study through 3 years.

G. Effectiveness Outcomes for Core Study

Effectiveness was assessed by cup/circumferential chest size measurements, patient satisfaction, and QoL. Mentor's patient satisfaction was based on a single question of "Would the patient have this breast surgery again?" The QoL measures were the Rosenberg Self Esteem Scale, the Body Esteem Scale, the Tennessee Self Concept Scale (TSCS), the SF-36, and the Functional Living Index of Cancer.

Primary Augmentation Patients

For primary augmentation patients, 370 (67%) out of the original 551 patients were included in the analysis of cup size at 3 years. Of these 370 patients, 359 (97%) experienced at least one cup size increase; the average increase in circumferential chest size was 2.8 inches.

At 3 years, 456 (83%) of the 551 patients enrolled completed the patient satisfaction question. Of these 456 patients, 445 (98%) stated to their surgeon that they would have the breast implant surgery again.

With regard to QoL measures through 3 years, an increase in self esteem was noted for 45% of patients after primary breast augmentation on the Rosenberg Self Esteem Scale. There was no change on the overall score of the Body Esteem Scale, but the Sexual Attractiveness Subscale and the Chest Score of the Body Esteem Scale increased. There was no change in the SF-36 after primary augmentation. There was no change in the overall score for the TSCS.

Revision-Augmentation Patients

For revision-augmentation patients, 116 (79%) out of the original 146 patients were included in the analysis at 3 years. For these 116 patients, the average increase in circumferential chest size was 2.4 inches.

At 3 years, 118 (81%) of the 146 patients enrolled answered the patient satisfaction question. Of these 118 patients, 111 (94%) stated to their surgeon that they would have the breast implant surgery again.

With regard to QoL measures through 3 years, no change in self esteem was noted following revision-augmentation surgery on the Rosenberg Self Esteem Scale. No changes were noted in the Body Esteem scale. There were no changes in SF-36. There was no change in the overall TSCS score.

Primary Reconstruction Patients

For primary reconstruction patients, 183 (73%) out of the original 251 patients were included in the analysis of circumferential chest size at 3 years. Of these 183 patients, the average increase in circumferential chest size was 1.3 inches.

At 3 years, 189 (75%) of the 251 patients enrolled answered the patient satisfaction question. Of these 189 patients, 185 (98%) stated to their surgeon that they would have the breast implant surgery again.

With regard to QoL measures through 3 years for primary reconstruction patients, a significant improvement in functioning was observed as measured by the Functional Living

Index of Cancer. No change was observed on Rosenberg Self Esteem Scale. There was no change in the overall score for the TSCS. There was no change on the overall score of the Body Esteem Scale. The Sexual Attractiveness Subscale of the Body Esteem Scale significantly improved. There was no change in any of the ten SF-36 scales.

Revision-Reconstruction Patients

For revision-reconstruction patients, 45 (76%) out of the original 59 patients were included in the analysis of circumferential chest size at 3 years. Of these patients, the average increase in circumferential chest size was 0.9 inches.

At 3 years, 48 (81%) of the 59 patients enrolled answered the patient satisfaction question. Of these 48 patients, 47 (98%) stated to their surgeon that they would have the breast implant surgery again.

With regard to the QoL measures through 3 years for revision-reconstruction patients, no change was observed on the Rosenberg Self Esteem Scale or in the Tennessee Self Concept Scale. For the Body Esteem Scale, two of six scales worsened over time, but, after adjusting for the aging effect, none of the changes were significant. The Sexual Attractiveness Subscale of the Body Esteem Scale significantly improved over time. Although some of the SF-36 scales showed decreases over time, after adjusting for the aging effect, changes in seven of ten SF-36 scales were not statistically significant.

XI. RUPTURE RATE AND CONSEQUENCES OF RUPTURE

To assess the rupture rate and consequences of rupture[*], FDA performed an extensive review of all available clinical and preclinical data. The clinical data included the Mentor Core Study, the Sharpe/Collis Study, the Mentor Adjunct Study, and the published literature. The preclinical data related to rupture included the retrieval study and fatigue testing. The FDA determined that, when the totality of the rupture data is considered, Mentor provided sufficient valid scientific evidence to support a reasonable assurance of safety and effectiveness of their product. These major data sources for rupture are briefly discussed below.

A. Mentor Core Study

While Section X above provided the rupture rates, this section include additional details regarding rupture in the Mentor Core Study. Mentor's Core Study included rupture rate data from the MRI cohort (original sample size of 420 who had scheduled MRIs to screen for silent rupture) at years 1 and 2 and from the non-MRI cohort (original sample size of 587) at years 1, 2, and 3. All reported ruptures were from patients in the MRI cohort. The rupture rates were 0.5% for primary augmentation, 7.7% for revision-augmentation, 0.9% for primary reconstruction, and 0% for revision-reconstruction through 3 years. There were a total of 8 ruptured/suspected ruptured implants in 6 patients through 3 years. Two of the implants were explanted and confirmed to be ruptured; the remaining 6 were considered

[*] Consequences of rupture include intracapsular rupture (when the gel remains within the scar tissue capsule surrounding the implant), extracapsular gel (when the gel moves outside the capsule but remains within the breast tissue), migrated gel (when the gel moves beyond the breast), and clinical consequences.

ruptured based on MRI evaluation. Of the 8 ruptured/suspected ruptured implants, 4 showed intracapsular gel and 4 showed extracapsular gel. There were no cases of migrated gel.

In summary, the Mentor Core Study, which was the primary source of rupture rate data for the Mentor product, provided compelling data demonstrating low rates of rupture through 3 years.

B. Sharpe/Collis Study

Mentor submitted the Sharpe/Collis Study, a European study, to provide information characterizing the rupture rate over a longer period of time than had been evaluated in the Core Study, as well as to provide supplemental information on the consequences of rupture. Silent rupture data were collected via a single MRI on 101 augmentation patients. The average age of the implants was approximately 9 years. Silent rupture was found in approximately 10% of these augmentation patients, which includes one patient for which the device was not explanted to confirm rupture. All ruptures were intracapsular (in other words, there were no cases of extracapsular rupture or migrated gel).

FDA acknowledges that the Sharpe/Collis Study is of limited value in providing a precise estimate of the long-term rupture rate. However, using the same framework discussed by the April 2005 Panel in assessing rupture, we determined that this study, which involved the specific devices for which approval was sought, provided valuable information to help characterize the long-term rupture rate and consequences of rupture. The study showed a relatively low rate of rupture at an average of 9 years for the women in the study. As with the Mentor Core Study, the low rates of rupture limited our ability to assess the consequences of rupture. However, the data we do have suggest that, when rupture does occur, gel migration is unlikely.

C. Mentor Adjunct Study

Although the Adjunct Study was neither designed nor intended to be the main set of clinical data to support the PMA, it provided important data assessing local complications associated with the devices. The studies showed that the local complications reported for women with ruptured implants were similar to those reported for women with intact implants.

D. Literature

Although the studies from the scientific literature were not device-specific, they collectively reported a large number of ruptures and, for that reason, provided important information about the consequences of rupture. Below is a summary of the key literature related to the consequences of rupture.

> Studies of Danish women evaluated with MRI involving a variety of manufacturers and implant models showed that about three-fourths of implant ruptures are intracapsular and the remaining one-fourth is extracapsular.[13] Additional studies of Danish women indicate that over a 2-year period, about 10% of the implants with intracapsular rupture progressed to extracapsular rupture as detected by MRI.[14] This means that for women with silicone gel rupture within the scar tissue capsule detected via MRI after 2 years, 1 in 10 of these women had progression of the gel outside the scar tissue capsule.

Approximately half of the women whose ruptures had progressed from intracapsular to extracapsular reported that they experienced trauma to the affected breast during this time period or had undergone mammography. In the other half, no cause was given. In the women with extracapsular rupture, after 2 years, the amount of silicone seepage outside the scar tissue capsule increased for about 14% of the women. This means that for 100 women with silicone gel rupture outside the scar tissue capsule, the amount of gel outside the scar tissue capsule increased for 14 women 2 years later. This type of information pertains to a variety of silicone implants from a variety of manufacturers and implant models, and it is not specific to Mentor's implants.

Below is a summary of information related to the health consequences of implant rupture, which have not been fully established. These reports were in women who had implants from a variety of manufacturers and implant models.

- Local breast complications reported in the published literature that were associated with rupture include breast hardness, a change in breast shape or size, and breast pain. These symptoms are not specific to rupture, as they also are experienced by women who have capsular contracture.

- There have been rare reports of gel movement to nearby tissues such as the chest wall, armpit, or upper abdominal wall, and to more distant locations down the arm or into the groin. This has led to nerve damage, granuloma formation, and/or breakdown of tissues in direct contact with the gel in a few cases. There have been reports of silicone presence in the liver of patients with silicone breast implants. Movement of silicone gel materials to lymph nodes in the axilla also has been reported, even in women without evidence of rupture, leading to lymphadenopathy.

- Concerns have been raised over whether ruptured implants are associated with the development of connective tissue or rheumatic diseases and/or symptoms such as fatigue and fibromyalgia.[15,16,17,18] A number of epidemiology studies have evaluated large populations of women with breast implants from a variety of manufacturers and implant models.,,,[19,20,21,22,23,24] However, other than one small study, these studies do not distinguish whether the women had ruptured or intact implants. These studies do not, taken together, support an association of breast implants with a typical, diagnosed rheumatic disease.

E. Retrieval Study and Fatigue Testing

As described in Section IX, Part D, above, the current retrieval study data showed that, through approximately 10 years, devices are not rupturing from pure cyclic fatigue (e.g., normal wear and tear). Rather, the data showed that the majority of device ruptures were surgically related and, thus, should be minimized by adequate physician training. Given, as discussed below, that failure from pure cyclic fatigue is not expected for several decades, the data show that there should not be an unexpected increase in failure rate through approximately 10 years due to design or materials defects.

Mentor used the raw data from their fatigue testing in a mathematical model that adjusted for the load/stress from walking, jogging, running, lying face down, and shell wrinkling.

The results from this model demonstrated that the devices can withstand lengthy cyclic loading for decades without failure due to inherent design or material flaws.

These data provide important information to help characterize the longer-term rupture rate of the Mentor product. Furthermore, as a condition of approval, FDA is requiring Mentor to continue their preclinical studies to continue to evaluate the modes and causes of rupture. These studies include, but are not limited to, long-term types of rupture, how localized stress occurs, the timing of instrument damage, and the correlation between surgical factors and device rupture. Any pertinent information will be added to the labeling. In addition, as another condition of approval, Mentor is required to limit access of their device to physicians who are trained on the implantation of their device. This is required in order to better assure that rupture rates due to surgical implantation factors are reduced. Depending on the findings of the postapproval modes and causes of rupture studies, FDA may require further physician training and/or device modifications.

XII. SUMMARY OF OTHER CLINICAL INFORMATION

The literature was also used to assess:

- connective tissue disease, signs, and symptoms
- cancer and benign breast disease
- neurological disease, signs and symptoms
- interference of device with mammographic detection of tumors or rupture
- ability to lactate
- offspring issues (safety of milk for breastfeeding and second generation effects)
- potential health consequences of gel bleed
- suicide risk.

The literature does not support a link between breast implants and any of the clinical concerns listed above. Refer to the patient labeling for a summary of the key literature related to the bulleted topics above.

XIII. PANEL RECOMMENDATION

At an advisory meeting held on April 11-13, 2005, the General and Plastic Surgery Advisory Panel recommended, in a 7 to 2 vote, that Mentor's PMA for the Mentor MemoryGel™ Silicone Gel-Filled Breast Implants be approved subject to the following conditions:

- continuation of Core Study and update Panel in 5 years
    - amend Core Study to include patients who had their device(s) removed; re-consent them and add connective tissue disease signs and symptoms
    - add independent monitoring committee to Core Study

- continuation of Adjunct Study and update Panel in 5 years

- voluntary registry – suggested including MRI data (including MRI screening method and frequency), connective tissue disease data, children of mothers with breast implants, pregnancy data, and mammography data)

- educational component that is required for access to device (detailed, simulated implantation or hands-on to demonstrate proficiency; board-certified or board-eligible)

- informed decision process

- modified labeling:
  - specify MRI scan at year 5 and every 2 years, thereafter
  - recommend removal if silent rupture detected
  - add statement reminding patients not to neglect regular mammography screening

- all postmarket commitments cited by Mentor at the April 2005 Panel meeting (except those specifically discussed in more detail by Panel). Proposed commitments cited were: continuation of Core Study to 10 years with data provided annually; a patient registry; a focus group study to assess patient labeling; continued commitment to formal, signed informed consents; physician training; and continued commitment to physician and patient education

- mandatory tracking.

XIV. CDRH DECISION

CDRH concurred with the Panel recommendation of April 2005, and issued a letter to Mentor on July 28, 2005, advising that its PMA was approvable subject to Mentor addressing issues related to postapproval conditions and labeling. The issues identified by FDA included revising the indications for use to limit augmentation to women who were at least 22 years old, providing additional Adjunct Study information on potential health consequences from rupture, stratifying the revision data into revision-augmentation and revision-reconstruction indications, establishing the recommendation for the method and frequency of screening for silent rupture, modifying the physician labeling, modifying the patient labeling, developing a patient informed decision process, revising the Core postapproval study protocol, revising the physician training program, and addressing the registry issue. Mentor submitted a response to the approvable letter in August 2005, after which FDA continued to develop the postapproval plans and labeling with the sponsor.

As part of the development of the final conditions of approval for this PMA, FDA considered not only the Panel input, but also the available clinical data, issues that should be further evaluated, and our experience with postapproval studies for saline-filled breast implants.

FDA followed the April 2005 Panel's recommendation regarding:

- continuation of the Core Study; however, the study has been modified to require MRIs every 2 years on all patients and to collect data on patients who had their device(s) removed
- continued follow-up of currently-enrolled Adjunct Study patients through 5 years with no new enrollment

- focus group study of patient labeling
- informed decision process
- modified labeling [prior to approval, Mentor was required to modify their labeling: (1) to include a statement that MRI scans should be performed at 3 years and every 2 years, thereafter; (2) to recommend implant removal if silent rupture is detected; and (3) to remind patients about regular mammography screening]
- mandatory tracking
- a physician training program that includes a certification of participation prior to having access to their product
- FDA will update the Panel on the status of the conditions of approval at years 5 and 10, as well as any other time deemed necessary by FDA if significantly new information from the postapproval studies become available.

In addition, FDA addressed the remaining conditions of approval recommended by the April 2005 Panel as follows:

- in lieu of a voluntary registry, FDA is requiring a large postapproval study (see below for details)
- an independent monitoring committee was not considered necessary for completion of the Core Study.

FDA issued an approval order on November 17, 2006. The final conditions of approval cited in the approval order are described below.

1. Mentor must continue their Core Study until all patients have completed their 10-year evaluation in order to assess the long-term clinical performance of their product. Data are to be collected via annual physician follow-up evaluations. The primary changes to the protocol from premarket to postapproval are that all non-MRI patients will have a MRI at years 6, 8, and 10 and that all patients who were explanted without replacement will be evaluated through 10 years, as per the protocol. Mentor must also update their patient and physician labeling to reflect 5 and 10-year Core Study findings, as well as any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

2. Mentor must conduct the 10-year large postapproval study, as per the protocol that was submitted to FDA on September 26, 2006. This study, which will begin patient enrollment within 90 days of PMA approval, will be a separate study from the Core Study and will include 41,900 Mentor silicone gel patients and 1,000 saline-filled breast implant patients as the control group. The purpose of this study is to address specific issues for which the Core Study was not designed to fully answer, as well as to provide a real-world assessment of some endpoints. The endpoints include long-term local complications, connective tissue disease (CTD), CTD signs and symptoms, neurological disease, neurological signs and symptoms, offspring issues, reproductive issues, lactation issues, cancer, suicide, mammography issues, and MRI compliance and rupture results. Data are to be collected via annual patient questionnaires, either completed via the web, mail, or telephone. There will also be physician evaluations at years 1, 4-6, and 9-10 to collect local complication data.

Mentor must update their patient and physician labeling to reflect 5 and 10-year large postapproval study findings, as well as any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

On a quarterly basis, Mentor must submit a report to FDA that includes: (1) the number enrolled by implant group (silicone versus saline); (2) the number enrolled by indication (primary augmentation, revision-augmentation, primary reconstruction, revision-reconstruction) and implant group; (3) the number enrolled by race/ethnicity and implant group; (4) the enrollment rate compared to the stated goals; and (5) the follow-up rates compared to the stated goals. The quarterly reports must continue to be submitted until FDA determines that they are no longer necessary.

Every 6 months for the first 2 years and then annually, thereafter, Mentor must submit a progress report that includes: (1) the status of patient enrollment as it compares to the stated goals; (2) the status of the race/ethnicity distribution as it compares to the stated goals; (3) detailed patient and device accounting; (4) a summary of findings for all study endpoints; and (5) the reasons why eligible patients were not enrolled into the study.

3. Mentor must continue preclinical studies to characterize the long-term modes and causes of failure of explanted retrieved devices for the 10-year duration of the large postapproval study. In addition, Mentor must perform additional studies to address the following specific issues:
    - further evaluation of iatrogenic failures to address issues raised by the April 2005 Panel
    - the characterization of when surgical instrument damage occurs
    - further evaluation and characterization of failures due to localized shell stress
    - any correlation between surgical factors (e.g., incision size) and device rupture.

    Mentor must also update their patient and physician labeling to reflect any relevant findings.

4. Mentor must complete a focus group study of the augmentation and reconstruction patient labeling. This will involve an independent group obtaining responses from patients on the format and content of the approved labeling. Upon completion of the focus group study, Mentor must provide a supplement with a report of the focus group study findings and revised patient and physician labeling based on those findings.

5. As part of their formal informed decision process, Mentor must distribute their approved patient labeling. Both the physician and the patient are intended to sign designated sections in order to best assure that a patient has obtained the labeling in an adequate enough time prior to surgery to read it and has understood the risks and other information associated with the Mentor device. Mentor administer their approved survey to a random selection of 50 physicians on an annual basis to determine the success of this process and provide a summary of the survey findings

to FDA. FDA will inform Mentor when a survey summary is no longer necessary. In addition, Mentor is to provide training on this process as part of their physician training program.

6. The Mentor Adjunct Study (P910037 and P910038) was designed to serve a public health need for reconstruction and revision patients. Because the public health need does not exist upon approval of this PMA P030053, Mentor is required to: (1) cease new patient enrollment into the Mentor Adjunct Study and (2) continue the follow-up of all currently-enrolled Mentor Adjunct Study patients through 5 years. These data are to be reported as part of the PMA annual reports for P030053.

A separate mandatory tracking order was issued on November 17, 2006.

In addition, completion of their physician training program is required as a condition of access to their product. FDA will, however, allow a 90-day transition period for all current Core Study and Adjunct Study investigators, after which these physicians must also have completed the training program in order to have access to the Mentor product.

The sponsor's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

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