SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Smooth and Textured Saline-Filled Mammary Prostheses

Device Trade Name: Saline-Filled and Spectrum® Mammary Prostheses

Applicant: Mentor Corporation
201 Mentor Drive
Santa Barbara, California 93111

Premarket Approval (PMA) Application Number: P990075

Date of Panel Recommendation: March 1, 2000

Date of Good Manufacturing Practice Inspection: May 10, 2000

Date of Notice of Approval to Applicant: May 10, 2000

II. INDICATIONS FOR USE

Breast implants are indicated for females for the following indications:

- Breast Augmentation. A woman must be at least 18 years old for breast augmentation.
- Breast Reconstruction.

III. CONTRAINDICATIONS

Patient Groups in which the product is contraindicated:

- Active infection anywhere in the body.
- Existing malignant or pre-malignant breast cancer without adequate treatment.
- Augmentation in women who are currently pregnant or nursing.

Surgical Practices which will compromise the product's integrity:

- Stacking of implants: Do not place more than one implant per breast pocket.
- Do not make injections into the implant.
- Do not alter the implant shell or valve.
- Do not place drugs or substances inside the implant other than sterile saline.
- Do not allow the implant to come in contact with Betadine®.

IV. WARNINGS

1. ***Closed Capsulotomy***
   DO NOT treat capsular contracture by forceful external compression, which may result in implant damage, deflation, folds, and/or hematoma. Capsule firmness must not be treated by over-expansion of the device.

2. ***Reuse***
   Breast implants are intended for single use only. Do not re-sterilize after package is opened.

3. ***Avoiding Damage during Surgery***
   - Care should be taken not to damage the prosthesis with surgical instruments.
   - Do not insert or attempt to repair a damaged prosthesis.
   - Use care in subsequent procedures such as open capsolotomy, breast pocket revision, hematoma/seroma aspiration, and biopsy/lumpectomy to avoid damage to the implant shell or valve.
   - Do not contact the implant with disposable, capacitor-type cautery devices.

4. ***Proper Filling***
   Follow the recommendation on the product data sheet for fill volume; do not overfill or underfill the implant.

5. ***Microwave Diathermy***
   The use of microwave diathermy in patients with breast implants is not recommended, as it has been reported to cause tissue necrosis, skin erosion and extrusion of the implant.

6. Do not use endoscopic/transumbilical approach in placement of the implant.

V. PRECAUTIONS

1. ***Specific Populations***
   Safety & Effectiveness has not been established in patients with:
   - Autoimmune diseases such as lupus and scleroderma
   - A compromised immune system (e.g., currently receiving immunosuppressive therapy)
   - Patients with conditions or medications which interfere with wound healing ability (such as poorly controlled diabetes) or blood clotting (such as concurrent coumadin therapy).
   - Reduced blood supply to breast tissue

2. ***Mammography***
   Breast implants may complicate the interpretation of mammographic images by obscuring underlying breast tissue and/or by compressing overlying tissue. Accredited mammography centers and use of displacement techniques are needed to adequately visualize breast tissue in the implanted breast.

   Presurgical mammography with follow-up mammogram 6 months to 1 year following surgery may be performed to establish a baseline for future routine mammography.

3. ***Radiation to Breast***
   Mentor has not tested the in vivo effects of radiation therapy on tissue of patients who have breast implants. The literature suggests that radiation therapy may increase the likelihood of capsular contracture, necrosis, and extrusion.

4. ***Long Term Effects***
   The long term safety and effectiveness of breast implants have not been studied; however, Mentor is monitoring the long term (i.e., 10 year) risk of implant rupture, reoperation, implant removal, and capsular contracture.

5. ***Instructions to Patients:***
   - ***Reoperation*** – Patients should be advised that additional surgery to their breast and/or implant will be likely over the course of their life.

- ***Explantation*** – Patients should be advised that implants are not considered life time devices and they will likely undergo implant removal, with or without replacement, over the course of their life. Patients should also be advised that the changes to their breast following explantation may be irreversible.
- ***Mammography*** - Patients should be instructed to inform their mammographers about their presence of their implants.
- ***Lactation*** – Patients should be advised that breast implants may interfere with the ability to successfully breast feed.
- ***Breast Examination Techniques*** - Patients should be instructed to perform breast self-examinations monthly and be shown how to distinguish the implant from their breast tissue. The patient should be instructed not to manipulate (i.e., squeeze) the valve excessively, which may cause valve leakage.

VI. DEVICE DESCRIPTION

The Mentor breast implants are constructed from RTV (Room Temperature Vulcanization) medical grade silicone elastomer. There are two families of implants – one referred to as the Saline-Filled Mammary Prostheses and the other referred to as the Spectrum® Mammary Prostheses.

The Saline-Filled family of implants has a self-sealing diaphragm valve on the anterior side of the implant that is used for filling the implant with sterile saline at the time of surgery.

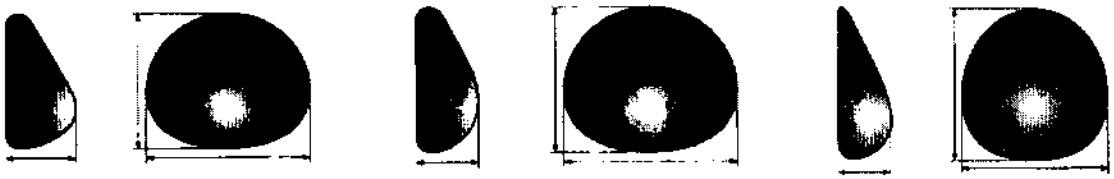
The Spectrum® family has a kink plug valve and a fill tube and injection dome on the posterior side of the implant that allows sterile saline to be added during surgery as well as after surgery. Once the desired volume is achieved, the fill tube and the injection dome are removed through a small incision under local anesthetic. A connector system is provided to join the pre-inserted fill tube to the injection dome. Two types of connector systems and injection domes are provided with each Spectrum implant, and either may be used.

Both the Saline-Filled and Spectrum implants are available with smooth, fully textured (Siltex®), and partially textured (PT) shell surfaces. The Siltex® texturing covers the entire shell. The partial texturing covers only the posterior side of the implant. The minimum thickness is 0.014" for the smooth and PT implants and 0.022" for the fully textured implants. It should be noted that the recently introduced PT shells were not included in the clinical studies. The PT shell texturing is different from the tested texturing in that the pores are fewer, but deeper, and the outward projections are fewer, but wider. The PT layer is made from a softer silicone.

The breast implant styles are as follows:

1600	Smooth	Round	-	125-700cc
2600	Siltex® textured	Round	-	125-475cc
2700	Siltex® textured	Contour	High	275-650cc
2900	Siltex® textured	Contour	Moderate	175-525cc
5000	Siltex® textured	Contour	Tall	150-700cc
5000 PT	Siltex® partially textured	Contour	Tall	150-700cc
1400	Smooth	Round	-	125-575cc
2400	Siltex® textured	Round	-	125-475cc
2500	Siltex® textured	Contour	High	275-650cc
6000	Siltex® textured	Contour	Tall	150-700cc
6000 PT	Siltex® partially textured	Contour	Tall	150-700cc

The following diagrams illustrate the high, moderate and tall contour profiles.



Contour, high profile Contour, moderate profile Contour, tall profile

All implants are provided sterile. All implants can be sterilized by dry heat. This sterilization method is validated for a sterility assurance level (SAL) of 10^{-6}. Additionally, Style 1600 will be provided sterile by a second alternative method of gamma radiation (a minimum of 2.5 MRad).

VII. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative treatments include, but are not limited to, external implants; autogenous tissue grafts; tissue flaps (e.g., transverse rectus abdominis muscle, latissimus dorsi muscle, gluteal muscle), or no treatment. For reconstruction or revision patients, an alternative treatment may be to receive silicone gel-filled implants through one of the controlled, on-going clinical studies.

VIII. MARKETING HISTORY

Saline-filled breast implants are preamendment devices and have been on the market since 1965. Mentor Corporation began marketing saline-filled mammary prostheses in April of 1984, following acquisition of the products from American Heyer-Schulte, who sold and distributed the products from 1972 until the Mentor acquisition. Mentor submitted a PMA in response to the final rule published in the Federal Register on August 19, 1999 (64 FR 45155), requiring manufacturers of saline breast implants to submit PMAs within 90 days.

IX. POTENTIAL ADVERSE EFFECTS

The following is a list of potential adverse events that may occur with breast implant surgery. The risks include: implant deflation/leakage, additional surgery, capsular contracture, infection, Toxic Shock Syndrome, necrosis, hematoma, seroma, extrusion, breast pain, changes in nipple sensation, changes in breast sensation, dissatisfaction with cosmetic results (wrinkling, folding, displacement, asymmetry, palpability, visibility, ptosis, sloshing), calcific deposits, irritation/inflammation, delayed wound healing, hypertrophic scarring, breast tissue atrophy/chest wall deformity, difficulty/inability in breast feeding, and inability to adequately visualize breast lesions with mammography.

In addition to these potential adverse events, there have been concerns with certain systemic diseases.

- **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 several large epidemiological studies of women with and without implants indicates that these diseases are no more common in women with implants than those in women without implants.

- **Cancer**
  Published studies indicate that breast cancer is no more common in women with implants than those without implants.

- **Second Generation Effects**
  There have been concerns raised regarding potential damaging effects on children born of mothers with implants. A review of the published literature suggests that the information is insufficient to draw definitive conclusions.

X. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies are divided into three sections: Chemistry Data, Toxicology Data, and Mechanical Data. Mentor changed vendors for their silicone materials after the completion of the clinical trial, but provided chemical, toxicological, and mechanical data to support the equivalence of the materials from the old and new sources.

A. Chemistry Data

1. **Materials** - The elastomer shells for both the Saline-filled and the Spectrum are made of a room temperature vulcanized (RTV) silicone containing linear silanol end-blocked polydimethylsiloxanes with a stoichiometric excess of methyltriacetoxysilane. Dibutyltin dilaurate is used as the catalyst. Fumed amorphous silica treated with hexamethyldisilazane is added to the mixture to provide strength to the elastomer.

2. **Concentrations of Low Molecular Weight Components** - The table below gives the amounts of various low molecular weight components present in the device shells. The data in the table were obtained from devices made from the new source. The

techniques used to isolate and detect these components included purge and trap or solvent extraction followed by gas chromatography-mass spectrometry, and solvent extraction with gel-permeation chromatography. Complete devices were extracted, so all implant components are represented.

The data shown were selected to illustrate the range of data available, and to provide the levels of some potentially toxic compounds. Cyclic-octamethyltetrasiloxane (D4) is more toxic than D3 or D5, but data for the closely related compounds are included. The higher cyclic siloxanes are considered nontoxic. The group of analytes shown contains volatile compounds such as isopropanol, the solvents toluene and xylene. Polychlorinated biphenyls (PCBs), which could have arisen from the bis(2,4-dichlorobenzoyl) peroxide used as a polymerization initiator in a minor device component was not detected.

Metal analyses were conducted for extractable inorganic metallic and organometallic compounds. Metals were extracted into aqueous buffers for 120 hours at 37°C, and the organometallics were extracted with a Soxhlet extractor into methylene chloride for 20 hours. The levels of metal (µg/g) were determined using inductively coupled plasma (ICP) atomic emission spectroscopy and cold vapor atomic absorption (CVAA). The levels reported in the table below are the sums of the inorganic and the organometallic compounds.

Concentrations of Low Molecular Weight Components (amu ≤ 1500)

Identification	Molecular Weight (amu)	Smooth Saline Shell (µg/g)
D3	222	0.97
D4	296	6.36
D5	370	12.35
D6	444	<6.3*
D10	740	90.4*
D15	1110	347.3*
D20	1480	62.3*
Isopropanol	60.09	1.88
Toluene	92.13	0.03
Xylenes	106.2	3.89
Metals		
Tin	118.7	0.5
Platinum	195.1	0.78
Arsenic	74.9	ND
Lead	207.2	ND
Zinc	65.4	0.26
Total Extractables (methylene chloride)		2.11%

* Methylene Chloride extraction

3. **Extent of Crosslinking** - Crosslinking was determined by measuring the swelling ratio of the shell in toluene, and the weight of the non-crosslinked material extracted by the solvent. The swelling ratio decreases for about 15 days after dipping. Smooth shells cured for 7 days have a crosslink density of 8.3×10^{-5} mole/cm^3 and a swelling ratio of 4.30.

The textured shells are the same shells with a textured layer attached by curing at 375°F. After 180 minutes of heating, the swelling ratio is 4.06. After sterilization by radiation, the swell ratio was 3.68 for the smooth device. This decrease from 4.06 reflects the effect of radiation. The finished sterilized device is close to maximally crosslinked.

Other data demonstrated that the decrease in swelling roughly parallels the decrease in extractable residue.

B. Toxicology Data

1. **Pharmacokinetics** – Pharmacokinetic studies were not required for three reasons: a. even if all of the low molecular weight toxic compounds were immediately released from two implants, the systemic concentrations would be too low to raise concern. b. the production of elastomer particles might produce local inflammation, but would not be distributed systemically; and, c. the conversion of amorphous silica to more toxic forms followed by subsequent release is extremely unlikely, but would also be local. Each of these issues is discussed below:

   a. The concentrations of toxic components were determined in the chemical analyses. The levels of all of these compounds are well below the toxic levels observed in laboratory animals or humans, based on the available literature.

      FDA assessed the exposure levels to potential toxicants, assuming all the toxicant is released to the systemic circulation at once. We used the residual levels of toxicants in the devices from the analytical data and safety information provided by Mentor or available in the toxicological the literature. Some of the assessments are summarized below.

      For cyclic-octamethyltetrasiloxane (D4), the amount per gram of implant was 6.36 μg. The total D4 in the largest device (Siltex Spectrum, weighing 48.3 g) would be 307 μg. The exposure level for a 60kg woman with two of the largest implant would be 614 μg total or 10.2μg/kg, if all the D4 were released at once.

      In rat studies conducted by Dow, the no adverse effect level for D4 for a reversible increase in liver weight was 12 mg/kg. Using safety factors of 10 for the species difference and a safety factor of 10 for the route of entry difference, the no observed adverse effect level (NOAEL) would be 0.12 mg per kg, well above the level of 10.2 μg/kg. Reproductive effects were not seen below 80mg/kg. Because of the diffusion limitation, far less than 10.2 μg/kg could be released immediately. The diffusion estimate is that only 0.44 μg/kg could be released over a 30-day period. The expected exposure to D4 is well below toxic levels.

      The exposure to metals from the implants was assessed assuming all the metals are released at once. Analyses were performed for antimony, arsenic, barium, beryllium, cadmium, chromium, cobalt, copper, lead, magnesium, mercury, molybdenum, nickel, platinum, selenium, silver, tin, titanium, vanadium, and zinc. In most case none were detected, or the levels were below the limit of

detection for the method used. The results of analyses for some of the metals of potential toxicological interest are summarized.

Platinum - This was detected in only one of 3 replicates at 0.78μg/g, close to the detection limit of 0.56μg/g. The worst case would be the release of 75 μg from 2 of the largest implants (48.3 g/implant), or 1.3 μg/kg in a 60 kg woman. The lowest intravenous toxic dose (TDLo) for cis-diaminedichloroplatinum is 500μg/kg, which corresponds to 325μg/kg of platinum, providing a 250-fold margin of safety.

Tin - The issue is dibutyltin dilaurate, which is used as a catalyst to polymerize the dispersion. Tin was detected at 0.5μg/g. If this were released at once from two of the largest implants, this would correspond to 60μg of tin, or 300μg of dibutyltin dilaurate. The intraperitoneal LD_{50} in rats for dibutyltin dilaurate is 8.5mg/kg. The safety factor here is 1700 fold.

Zinc - This was detected in several samples at 0.25μg/g or less. One set of samples had levels of 12μg/g. This highest level would release 1440μg. This essential nutrient is present in the body at 1.4 to 2.3g, so no toxicity would be expected. Even with the highest sample, the blood level would remain within normal bounds. The reason for the high spurious result is not clear.

b. Elastomer particles were implanted in the 2-year chronic toxicity/carcinogenicity study. No evidence of systemic toxicity or unusual local toxicity was observed. The particle size was less than 1 mm, but the size distribution was not provided. Very small particles produced by abrasion might produce local inflammation.

c. Amorphous silica can not be converted to crystalline forms in the device, though Mentor cited one reference with theoretical reasons why some conversion of silica to other forms may occur. Two other references cited showed that amorphous silica was not present at the surface of the shell. No amorphous silica could leave the shell. The shell has not been demonstrated to be cytotoxic.

There are no pharmacokinetic issues remaining from the chemical analysis of the devices because the worst-case exposures are well below the toxic levels.

The toxicity testing data shown below were obtained from materials made from the old source. Mentor has provided data demonstrating equivalence of the devices made from either source.

2. **Cytotoxicity**

- Direct Contact Method - Silicone elastomer was tested by placing 1 cm^2 of the material directly on the agarose overlay and incubated on L-929 mouse fibroblasts for 24 hours. No lysis or toxicity was seen. Normal growth was observed in the USP negative control, and a 4 mm zone of lysis was seen near the positive control (NamSA Latex #14 or #15). Several of the silicone elastomers and adhesives used in the smooth saline implant with a diaphragm valve and the Siltex implant with diaphragm valve were tested. The materials were all considered nontoxic.

- MEM Elution Method - This test was performed on an extract of a smooth saline implant with a diaphragm valve, and on a Siltex implant with diaphragm valve. The implants, 37.4 cm^2, were extracted with 12 ml of 5% MEM for 24 hours at 37°C. No toxicity was seen except in the positive controls.

3. **Intracutaneous Toxicity** - Tests were performed on both the smooth and Siltex (Textured) Implants. Samples, 37.4 cm^2, of each device were extracted for 24 hours at 37°C into 12 ml of saline and into 12 ml of cottonseed oil. For testing, 0.2 ml of each extract was injected intracutaneously into rabbits. The extracts of the test articles were compared with injections of the solvents without test article on the other sides of the same animals. Skin reactions to the test and control extracts were compared. No reactions were seen with the saline extracts. The cottonseed oil extracts produced barely perceptible edema, and barely perceptible to defined erythema. In no case was the reaction of the test articles stronger than the negative control. There was no significant intracutaneous toxicity.

4. **Implantation** - This was conducted as part of the 2-year carcinogenicity study. There was no evidence of systemic toxicity as evidenced by mortality rate, weight gains, organ weights, hematology, or serum chemistry. The gross and histological changes at the implantation site were consistent with foreign body reactions.

5. **Acute Systemic Toxicity** - Acute systemic toxicity was studied in the smooth and Siltex (textured) saline implants. Samples, 37.4 cm^2, of each device were extracted for 24 hours at 37°C into 12ml of saline and into 12 ml of cottonseed oil. The controls were the same solvents treated the same way, but without a test article. Each extract and control were injected into groups of 5 mice. The mice, 17 to 23 g, were observed immediately, and at 4, 24, 48, and 72 hours. Body weights, reactions, and mortalities were recorded. There were no mortalities, reactions, or significant differences in weight.

6. **Hemolysis** - Hemolysis was measured by two methods. In the direct method, the test material was mixed with whole rabbit blood in saline. After incubation for 1 hour at 37°C, the suspension was centrifuged, and hemolysis was determined by measuring the absorbance of the supernatant solution at 545 nm. The positive control was distilled water to suspend the cells, and the negative control was saline.

   The second method used saline extracts of the test material to test for hemolysis. Six grams of the test material were added to 30 ml of saline, and incubated for 72 hours at 50°C. The extract solution was added to a suspension of rabbit cells in saline, and hemolysis was measured as above.

   The several elastomer types and adhesive, a smooth implant with a diaphragm valve, and a Siltex implant with a diaphragm valve were tested. No significant hemolysis was seen.

7. **Immunotoxicity**
   - Sensitization –
     a. Several implant components and a smooth and textured implant were tested for sensitization in the Magnusson and Kligman assay. Four grams of test article were extracted with 20 ml of saline for 72 hours at 50°C. The

extracts were injected intradermally in Guinea pigs. The silicone showed no positive responses in the 8 test animals. The positive control, 1-chloro-2,4-dinitrobenzene (DCNB), was positive. None of the test items was sensitizing. The tests were performed with saline extracts of the test articles. The breast implants were tested with 60 cm^2 per 20 ml. Both saline and cotton seed oil extracts were tested.

b. An RTV textured shell and an RTV smooth shell were tested. The Magnusson Kligman method was used, with DCNB as the positive control. Extracts were made using a ratio of 120 cm^2 of the device per 20 ml of extraction vehicle at 121°C for 1 hour. The vehicles used were 0.9% saline and cottonseed oil. None of the animals challenged with test material was sensitized, but all of the positive control animals were sensitized.

- Sensitization testing for the Spectrum Device – 120 cm^2 of smooth or textured RTV silicone elastomer were tested for sensitization in the Magnusson and Kligman assay. The test materials were extracted with 20 ml of saline or cottonseed oil for 1 hour at 121°C. The extracts were injected intradermally in Guinea pigs. The silicone showed no positive responses in the test animals. The positive control, 1-chloro-2,4-dinitrobenzene (DCNB), was positive. None of the test items were sensitizing.

  For the remaining immunotoxicity tests, the sponsor indicated that the elastomer was obtained from sterilized final product, no washing steps were used, and the elastomer was ground in liquid nitrogen, so volatile compounds were retained. There is no reason to believe that potential immune stimulators were removed from the elastomer before testing.

- Adjuvant Effect of Silicone Elastomer - Sixty rats were immunized with bovine serum albumin (BSA) on day one. Anti-BSA antibodies were measured 55 days later using an ELISA. The rats were divided into seven groups, based on the adjuvant or test material accompanying the BSA. The control was saline plus BSA only. In addition to BSA and saline (G), the test groups each got one of the following: Incomplete Freund's adjuvant (IFA), silicone oil, IFA and silicone oil, 50% silicone gel and 50% silicone oil, silicone oil and 1000 micron elastomer particles, or silicone oil plus 500 micron elastomer particles. The elastomer particles were from a Siltex saline shell with a leaf valve. Only the IFA, the IFA plus silicone oil, and the silicone oil and silicone gel produced significant levels of anti-BSA antibodies. Silicone gel was not tested by itself. The elastomer particles did not act as an adjuvant, even in the presence of silicone oil.

- Cellular Immune Responses - Effects of the smooth RTV shell and a textured low bleed shell (included for texture material) on Immune System - Female B6C3F1 mice got subcutaneous implants of the tested shells at 14, 28, or 57mm^2. The elastomers were obtained from sterilized final product. The animals were exposed to the subcutaneous implants for 28 days. The negative controls were untreated and sham operated animals. Mice injected with cyclophosphamide were positive controls. The testing followed recommendations of the National Toxicology Testing Program.

There were no effects of implantation on body weight gain, spleen or thymus weights, thymus histology, numbers of red cells, MCV, MCH, MCHC, leukocytes, leukocyte differential count, B cell, T cells, or T-cell subsets. Responses to Concanavalin A, the mixed leukocyte response, and natural killer cell activity were normal. There were reduced levels of spleen IgM antibody forming cells, and a decreased response to lipopolysaccharide. Neither of these reduced responses was biologically significant. The spleen cell response was seen at the low dose, but not at the two higher doses. The lipopolysaccharide response was only 10% less than the control at the low dose and 8% less at the high dose. The intermediate dose was not significantly different from the control.

8. **Bacterial Mutagenicity** - The mutagenic potential of the Saline-filled mammary prosthesis with a diaphragm valve (extracted at 120 cm^2 per 20 ml of solvent), the Siltex (textured) saline-filled prosthesis with a leaf valve, and the Siltex Spectrum prosthesis with tubing, connector system, micro fill valve, and standard fill valve, was tested in the Ames Salmonella assay. The assays employed a battery of 5 strains, and were conducted with and without microsomal activation. To prepare the extracts for testing, the devices were cut into small pieces, and put into 170 ml of saline or USP ethanol. The concentration was at least 4 g of test article per 20 ml of solvent. The saline extractions were performed by autoclave at 121°C for 60 minutes. The ethanol extractions were performed at 37°C for 24 hours. None of the devices produced a positive response with any of the tester strains.

9. **Mammalian Forward Mutation Assay** - The Mouse Lymphoma Mutagenesis assay was used to test for mutagenicity in mammalian cells. The test articles were the Saline-filled mammary prosthesis with the diaphragm valve, the Spectrum mammary prosthesis with tubing, connector system, micro fill valve, and standard fill valve, and the Siltex saline-filled mammary prosthesis with the Mentor leaf valve.

   The devices were extracted with saline and with ethanol at a ratio of 120 cm^2 of device per 20 ml of extraction medium (The USP standard for sheets less than 0.5 mm). The ethanol extract was incubated at 37°C for 24 hours, and the saline extraction was performed by autoclaving at 121°C for 1 hour. Controls were prepared the same way, without the device. The test employed L5178Y cells, and used trifluorothymidine as the restrictive agent. The test was performed with and without microsomal activation. All of the test extracts were negative in the presence and the absence of microsomal activation. EMS was used as a positive control for direct acting mutagens, and DMBA was the control for action-dependent mutagens. The positive controls met the criteria for positive tests.

10. **Unscheduled DNA Synthesis** - Unscheduled DNA synthesis was studied using the Siltex Spectrum with tubing, connector system, Micro fill valve, and standard fill valve, the smooth saline-filled prosthesis with the diaphragm valve, and the Siltex (textured) saline-filled prosthesis with Mentor leaf valve.

    The devices were extracted into saline and into ethanol based on a ratio of 4 g per 20 ml of solvent. The saline articles were extracted at 121°C for 60 minutes, and the ethanol extracts were incubated at 37°C for 24 hours. The alcohol was 100% USP Grade. The saline and ethanol extracts were both tested at 8 dose levels ranging from 0.01 to 10 µl/ml. The test article and control culture dishes each received 10µCi/ml of tritiated thymidine. The cells used were from primary rat hepatocyte cultures.

Toxicity was measured as the release of LDH, and unscheduled DNA synthesis was measured as the percentage of cells incorporating tritiated thymidine. None of the test extracts induced unscheduled DNA synthesis. The positive control, DMBA, produced a positive response.

11. **Cell Transformation Assay** - The cell transformation assay used was the morphological transformation of BALB/3T3 Mouse Embryo Cells. The following devices were tested: the saline-filled mammary prosthesis with the diaphragm valve, the Siltex (textured) Saline-Filled Mammary Prosthesis with the Mentor Leaf Valve, and the Siltex® Spectrum Post-operatively Adjustable Prosthesis, with tubing, connector system, Micro Fill valve, and standard fill valve.

The devices were extracted into saline and into 100% ethanol. The device was cut into small pieces, and extracted at a ratio of no less than 4 g per 20 ml of extraction medium. For the saline-filled and textured saline-filled devices, the extracts were from 120 cm^2 of the test article per 20 ml. The saline extract was at 121°C for 60 minutes, and the ethanol extraction was at 37°C for 24 hours. The cells were exposed to 4 concentrations of each of the extracts. The assays were conducted with a 3-day exposure in the nonactivated system and with a four-hour exposure in the S-9 microsome-activated system.

The devices were all negative in this test. None of the devices increased the proportion of transformed cells without or with activation. N-methyl nitrosoguanidine was the positive control without activation and dimethylnitrosamine was the positive control in the microsomal activation assay. The positive controls produced statistically positive results.

12. **2-Year RAT Carcinogenicity Study** - A 2-year implantation study was conducted in female Fisher 344 rats with weights of 110 to 160 g at the time of implantation. The test articles and the approximate doses of material implanted subcutaneously parallel to the spine are listed below:

Sham Control	0.6 ml sesame oil
RTV smooth shell with diaphragm valve	280 mg
RTV textured shell with leaf valve	430 mg.

The samples were prepared by freezing in liquid nitrogen, and grinding in a Warring blender filled with liquid nitrogen. The ground particles were sieved, and suspended in sesame oil for delivery.

There were 80 animals in each group; sixty in the main group and twenty reserved in a satellite group for clinical pathology, organ weights, and histopathology examinations at 3 and 12 months. The duration of the study was 24 months.

There was no systemic toxicity evidenced by mortality rate, weight gains, organ weights, hematology, and serum chemistry. The gross and histological changes at the implantation site were the commonly seen foreign body reactions. Rats from all implanted groups developed fibrosarcomas at the implant site. Solid foreign bodies produce these kinds of tumors.

Style No.	No. Samples Tested	Ave. Tear Strength (lbf)	Ave. Tear Strength (lbf/in)
1600	520	6.03	662
2600	401	5.86	566
2700	179	5.89	558
2900	195	6.15	575
1400	180	6.30	667
2400	231	7.19	645
2500	180	6.88	582

2. **Tear Resistance** - Testing was performed in accordance with ASTM D624. The prepared samples were subjected to tensile testing at 20 in/min until failure. The force at failure was recorded. The results presented below are pooled within a style (i.e., combined sizes, shell material, and sterilization method).

Style No.	No. Samples Tested	Ave. Tear Force (lbf)
1600	326	2.67
2600	185	4.22
2400	174	3.83

3. **Adhered Joint** – Patch/shell joint testing was performed in accordance with ASTM F703. As per ASTM F703, the pass/fail criterion was no failure after stressing the sample to 200% elongation for 10 seconds. All samples passed. Then the samples were taken to failure to determine the break force. All samples had a breaking force greater than 2.5 lbs, which is the ASTM F703 criteria for shells, not joints.

The results presented below are pooled within a style (i.e., combined sizes, shell material, and sterilization method).

Style No.	No. Samples Tested	Ave. Break Force (lbf)
1600	385	5.73
2600	293	5.57
2700	180	6.38
2900	180	6.65
1400	180	5.83
2400	180	6.39
2500	180	6.04

4. **Valve Competency** - A total of four different tests to assess valve competence were conducted on Mentor diaphragm and kink plug valves. Test methods were provided for 2 of the 4 tests - maximum burst pressure and functional test. The tests were:

- *Static* - The whole device was subject to a static internal pressure of approximately 1-1.3psi by placing a 15lb weight on the device for a prolonged period of time. This test was to determine the valve's stability to withstand a constant stress, which could induce failure due to valve material creep. All samples passed.

- *Dynamic* – Test samples consisting of the valve with a ring of surrounding patch/shell were cycled between 0 and 3 psi for 200,000 cycles (reported as equal to 10 times per day for 50 years). This test was to determine the valve's ability to withstand dynamic pressures roughly resembling the typical oscillations a device might experience *in vivo*. All samples passed.

- *Functional testing* – This test assessed filling the device with saline through the valve and the valve's sealing capability once the tube used to fill the device was removed. All samples passed.

- *Maximum burst pressure* – Test samples consisting of the valve with a ring of surrounding patch/shell were subject to increasing internal pressure until failure or rupture of the surrounding patch/shell. Samples were taken from the anterior valve/shell section of the diaphragm valve and the posterior patch/shell section of the kink plug valve.

The following data and discussion involve the maximum burst pressure testing. For simplicity sake, the results presented below are pooled across style (i.e., combined sizes, shell material, and sterilization method).

Style #	No. Samples Tested	Ave. Valve Burst Pressure (psi)
1600	538	21.2
2600	330	18.0
2700	180	18.1
2900	180	17.7
1400	180	25.0
2400	180	23.5
2500	180	24.2

It was noted that the diaphragm valves (styles 1600, 2600, 2700, and 2900) failed at lower pressures than the kink plug values (styles 1400, 2400, and 2500). The sponsor stated the reason is related to how the valves are attached to the shell. The failure mode during the maximum pressure testing is usually the rupture of the patch or shell that is attached to the valve for this test. With the diaphragm valves, shell rupture usually occurred where the valve is directly bonded to the shell or where one of the plug strap ends is directly bonded to the shell. With the kink plug valve, the failure was usually due to rupture of the patch that attaches the valve to the shell. The patch provides an additional layer of silicone sheeting over the shell thus accounting for the higher pressure needed to cause kink plug valve sample failure. The burst pressures are all above those expected to be experienced under normal implant conditions, as discussed below.

The following additional testing was performed to correlate these data to two *in vivo* conditions:

- In the first test, flat barbell weights were placed on top of filled diaphragm and kink plug valve devices with fill tubes still attached. The internal pressure was measured using a pressure gauge through the fill tube. The weight was increased from 0 to 50 lbs. It was reported that the 50 lb weight represents the load exert on the implanted device with a 200 lb woman sleeping on her

stomach, i.e., ¼ of her body weight; a 50 lb weight results in an internal pressure of 3psi.

- In the second test, internal pressures were recorded through a hypodermic needle inserted into the injection dome of the Spectrum device with people of various weights lying on the devices. It was reported that a 200 lb man with the smallest device (125cc) exerted an internal pressure of 3 psi as well. Midsize devices (375cc) exerted an internal pressure of <2 psi. Based on this data, the sponsor believed that 3 psi internal pressure is the worst case; therefore, the diaphragm valves have a safety factor of 5 to 7 times what is expected *in vivo* and the kink plug valves have a safety factor of 8 to 9 times.

5. **Static Rupture** - Static rupture testing was provided on sizes 175cc, 275cc, and 375cc of Style 2600. For this static compression testing, there was no failure/rupture because the maximum force of the testing jig was reached. Additionally, 3 of the samples were preconditioned prior to this testing, i.e., underwent fatigue cycling at 1 Hz to 10,000 cycles under a 50lb load. The average static loads ranged from 162lb to 334lb and reached the machine's maximum load capacity without device rupture. Even though worst case testing (smallest size with thinnest shell) was not provided, it is expected that the loads would still be much greater than that experienced in-vivo.

6. **Fatigue Rupture** – The fatigue rupture testing provided was considered incomplete because it was not performed on the worst case devices. The testing performed was compression fatigue testing in load control on Styles 2600, 2400, and 2500. The endurance load level for this testing ranged from 30 to 40 lbs.

As a condition of approval, the sponsor provided a protocol for new fatigue rupture testing of the worst case devices. Worst case testing would involve the thinnest shells of the smallest size determined by the manufacturing release criteria (e.g., individual thinnest measurement or average of measurements for shell). The following styles were identified as being worst case for each of the implant families:

Style	Surface	Size	Thickness
[illegible]			
1600	Smooth	125cc	0.014"
2600	Siltex® textured	125 cc	0.022"
5000 PT	Siltex® partially textured	150 cc	0.014"
[illegible]			
1400	Smooth	125 cc	0.014"
2400	Siltex® textured	125 cc	0.022"
6000 PT	Siltex® partially textured	150 cc	0.014"

Of these worst case devices above, fatigue rupture testing will be performed on Styles 1600 (gamma sterilized), 1600 (dry heat sterilized), 2600 (dry heat sterilized), and 5000 PT (dry heat sterilized), which will represent all subject implants. The device will be made with shells specifically manufactured to a thickness of 0.0125" to 0.0145".

Fatigue rupture testing is currently underway

stomach, i.e., ¼ of her body weight; a 50 lb weight results in an internal pressure of 3psi.

- In the second test, internal pressures were recorded through a hypodermic needle inserted into the injection dome of the Spectrum device with people of various weights lying on the devices. It was reported that a 200 lb man with the smallest device (125cc) exerted an internal pressure of 3 psi as well. Midsize devices (375cc) exerted an internal pressure of <2 psi. Based on this data, the sponsor believed that 3 psi internal pressure is the worst case; therefore, the diaphragm valves have a safety factor of 5 to 7 times what is expected *in vivo* and the kink plug valves have a safety factor of 8 to 9 times.

5. **Static Rupture** - Static rupture testing was provided on sizes 175cc, 275cc, and 375cc of Style 2600. For this static compression testing, there was no failure/rupture because the maximum force of the testing jig was reached. Additionally, 3 of the samples were preconditioned prior to this testing, i.e., underwent fatigue cycling at 1 Hz to 10,000 cycles under a 50lb load. The average static loads ranged from 162lb to 334lb and reached the machine's maximum load capacity without device rupture. Even though worst case testing (smallest size with thinnest shell) was not provided, it is expected that the loads would still be much greater than that experienced in-vivo.

6. **Fatigue Rupture** – The fatigue rupture testing provided was considered incomplete because it was not performed on the worst case devices. The testing performed was compression fatigue testing in load control on Styles 2600, 2400, and 2500. The endurance load level for this testing ranged from 30 to 40 lbs.

As a condition of approval, the sponsor provided a protocol for new fatigue rupture testing of the worst case devices. Worst case testing would involve the thinnest shells of the smallest size determined by the manufacturing release criteria (e.g., individual thinnest measurement or average of measurements for shell). The following styles were identified as being worst case for each of the implant families:

1600	Smooth	125cc	0.014"
2600	Siltex® textured	125 cc	0.022"
5000 PT	Siltex® partially textured	150 cc	0.014"
1400	Smooth	125 cc	0.014"
2400	Siltex® textured	125 cc	0.022"
6000 PT	Siltex® partially textured	150 cc	0.014"

Of these worst case devices above, fatigue rupture testing will be performed on Styles 1600 (gamma sterilized), 1600 (dry heat sterilized), 2600 (dry heat sterilized), and 5000 PT (dry heat sterilized), which will represent all subject implants. The device will be made with shells specifically manufactured to a thickness of 0.0125" to 0.0145".

Fatigue rupture testing is currently underway.

7. **Shelf-Life** - 5-year real-time product shelf life testing was performed on gamma sterilized Saline-Filled implants manufactured from the former material. Additionally, 5-year accelerated testing was performed on Spectrum implants manufactured from the former material. Five-year accelerated product shelf life testing was performed on dry heat sterilized Saline-Filled implants manufactured from the current material (Style 2600-textured and Style 1600-smooth). The physical testing was conducted on coupons and included patch to shell joint strength, tension set, valve burst pressure, shell break force, shell elongation, shell tear force, and energy to break. The package integrity testing was conducted on whole packaged devices and included peel strength, microbial barrier challenge, bubble emission test, and visual inspection.

   This shelf life testing was not representative of all of the final products, specifically, the kink plug valve of the Spectrum styles and gamma-sterilized implants were not tested. However, using the shelf-life data in conjunction with their clinical data demonstrated no exaggerated deflation rates. The current 4-year shelf life will remain on the label with the condition of approval that the sponsor complete their 5-year real-time shelf life testing for dry heat-sterilized devices (and gamma radiation for applicable smooth Saline-filled devices) on both the Saline Filled and Spectrum devices. This testing is to include (1) tensile, joint strength, ultimate elongation and valve competency testing on both the Saline-Filled and Spectrum devices to five years and (2) package integrity including microbial challenge, peel strength and dye penetration (bubble emission). This testing is currently underway.

XI. SUMMARY OF THE PROSPECTIVE CLINICAL STUDIES

A. Study Design

The safety and effectiveness of Mentor Corporation Saline-filled implants were evaluated in 2 prospective open label multicenter clinical studies: the Large Simple Trial (LST) and the Saline Prospective Study (SPS).

The LST Study was designed as an open label, one year study to assess the four safety outcomes of capsular contracture, infection, implant leakage/deflation, and implant removal for a large number of patients. Patients were those seeking breast augmentation, breast reconstruction, or revision of an existing implant for medical and/or surgical reasons. Follow-up visits occurred post-operatively at 0-6 weeks, 6 months, and at 12 months.

The SPS was designed as an open label, prospective, multicenter study of females undergoing breast augmentation or reconstruction who were negative for systemic lupus erythematosus, discoid lupus, and scleroderma as determined by the attending plastic surgeon, and who were negative for active cancer of any type for augmentation patients. Conditions for augmentation included post-partum mammary involution, correction of pseudo ptosis and/or mild asymmetry, and breast enlargement consistent with the personal desires of the patient. Conditions for reconstruction included post unilateral or bilateral mastectomy as a result of cancer or other disease process, post-trauma defined as total or partial removal or maldevelopment of the breast(s) through surgery (for any reason) or as a result of the trauma itself, profundus breast underdevelopment, congenital deformities of the chest cage (e.g. pectus excavatum, pectus carinatum), severe asymmetry defined as congenital or acquired substantial discrepancy in breast sizes (i.e. sufficient to require padding in one bra cup) such as to represent a significant physical deformity/abnormality

Table 1. LST: 1-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient.

	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Capsular Contracture III/IV	4.6%	(3.5, 5.7)	29.0%	(20.1, 37.8)	14.5%	(8.9, 20.1)
Implant Removal with or without Replacement	3.6%	(2.6, 4.5)	9.5%	(3.8, 15.3)	6.0%	(1.9, 10.2)
Leakage/Deflation	1.4%	(0.7, 2.0)	NA*	NA	2.3%	(0.0, 4.8)
Infection	0.9%	(0.5, 1.4)	NA	NA	NA	NA

*Insufficient numbers of patients to calculate a Kaplan-Meier risk rate.

D. Safety Outcomes of 1995 SPS

The SPS safety outcomes for primary implantation are presented in tables 2-4 below. Complications following implant removal with replacement (i.e., revision) are not included in Tables 2-4.

1. **Cumulative Kaplan-Meier Risk of First Occurrence of Adverse Events** - The cumulative Kaplan-Meier risk of first occurrence of adverse events (and 95% confidence interval) reported in greater than 1% of patients is shown in Table 2.

Table 2. SPS: 3-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient and By Implant.

	Augmentation				Reconstruction			
	By Patient		By Implant		By Patient		By Implant	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Wrinkling	20.8%	(18.4, 23.2)	19.7%	(18.0, 21.4)	20.0%	(15.4, 24.5)	20.1%	(16.7, 25.1)
Secondary Surgical Treatment	13.2%	(11.2, 15.2)	10.3%	(9.0, 11.6)	40.1%	(35.0, 45.3)	35.3%	(31.1, 39.6)
Loss of Nipple Sensation	10.2%	(8.4, 12.0)	7.5%	(6.4, 8.6)	34.5 %	(29.0, 40.0)	32.4%	(27.7, 37.2)
Capsular Contracture III/IV or grade unknown	9.0%	(7.3, 10.7)	6.8%	(5.7, 7.8)	30.0%	(24.5, 34.8)	28.3%	(23.9, 32.8)
Implant Replacement/ Removal for Any Reason	8.1%	(6.5, 9.7)	6.4%	(5.3, 7.4)	26.8%	(22.2, 31.5)	23.5%	(19.7, 27.4)
Asymmetry	6.7%	(5.2, 8.1)	N/A	N/A	27.9%	(23.0, 32.7)	N/A	N/A
Breast Pain	5.1%	(3.8, 6.5)	3.5%	(2.8, 4.3)	17.2%	(12.5, 21.9)	14.5%	(10.8, 18.2)
Intense Nipple Sensitivity	4.8%	(3.5, 6.1)	3.8%	(3.0, 4.6)	<1%	<1%	<1%	<1%
Leakage/Deflation	3.3%	(2.2, 4.5)	2.0%	(1.4, 2.6)	9.2%	(5.7, 12.7)	7.5%	(4.6, 10.3)
Hypertrophic Scarring	2.2%	(1.3, 3.0)	1.6%	(1.0, 2.1)	4.9%	(2.6, 7.2)	4.1%	(2.3, 5.9)
Infection	1.7%	(0.97, 2.5)	<1%	(0.57, 1.4)	9.0%	(6.0, 12.1)	7.9%	(5.4, 10.3)
Implant Palpability	1.6%	(0.88, 2.4)	1.6%	(1.1, 2.1)	<1%	-	<1%	-
Hematoma	1.5%	(0.80, 2.2)	<1%	(0.47, 1.2)	1.3%	(0.16, 2.4)	<1%	(0.12, 1.7)
Ptosis	1.5%	(0.80, 2.2)	1.4%	(0.9, 1.9)	<1%	-	<1%	-
Delayed Wound Healing	<1%	-	<1%	-	5.8%	(3.5, 8.1)	4.8%	(3.0, 6.6)
Implant Extrusion	<1%	-	<1%	-	2.4%	(0.72, 4.0)	1.7%	(0.52, 3.0)
Implant Malposition	<1%	-	<1%	-	1.1%	(0.02, 2.2)	1.0%	(0.13, 1.9)
Seroma	<1%	-	<1%	-	5.9%	(3.6, 8.3)	4.7%	(2.9, 6.5)
Tissue/Skin Necrosis	<1%	-	<1%	-	2.0%	(0.64, 3.4)	1.5%	(0.46, 2.5)
Irritation/Inflammation	<1%	-	<1%	-	7.6%	(4.6, 10.5)	5.8%	(3.5, 8.0)

2. **Types of Reoperation Procedures Through 3 Years** –

Table 3a. SPS: Types of Reoperation Procedures through 3 Years for Augmentation. Of the 1264 augmentation patients, there were 147 (11.6%) who underwent at least one reoperation procedure over the three years of follow-up in the SPS. A total of 358 reoperation procedures were performed in augmentation patients over the three years of the SPS. The types of reoperation procedures are shown below based on the number of procedures.

Types of Reoperation Procedures for Augmentation	N = 358 procedures	
	#	%
Implant Removal with Replacement	116	32%
Capsule Related[1]	77	22%
Scar or Wound Revision	67	19%
Reposition Implant	29	8%
Saline Adjustment	27	8%
Mastopexy	23	6%
Implant Removal without Replacement	9	3%
Biopsy/Cyst Removal	6	2%
Breast Reduction or Mastectomy	3	<1%
Nipple Related[2]	1	<1%
Total	**358**	**100%**

Notes: [1]Capsule procedures include open capsulotomy and capsulectomy.
[2]These were unplanned nipple procedures.

Table 3B. SPS: Types of Reoperation Procedures through 3 Years for Reconstruction - Of the 416 reconstruction patients in the SPS, 149 (35.8%) underwent at least one reoperation procedure over the three years of follow-up. A total of 353 reoperation procedures were performed in reconstruction patients over the three years. The types of reoperation procedures is shown below based on the number of procedures.

Types of Reoperation Procedures for Reconstruction	N = 353 procedures	
	#	%
Capsule Related[1]	99	28%
Implant Removal with Replacement	66	19%
Scar or Wound Revision	47	13%
Implant Removal without Replacement	40	11%
Nipple Related[2]	29	8%
Saline Adjustment	23	7%
Reposition Implant	20	6%
Biopsy/Cyst Removal	2	<1%
Breast Reduction or Mastectomy	2	<1%
Mastopexy	1	<1%
Total	**353**	**100%**

Notes: [1]Capsule related includes open capsulotomy and capsulectomy.
[2]These nipple procedures which were not part of planned reconstruction.

3. **Reasons for Implant Removal Through 3 Years** -

Table 4a. SPS: Reasons for Implant Removal through 3 Years for Augmentation - Of the 1264 augmentation patients, there were 87 patients (6.9%) who had 137 implants removed over the three years of follow-up in the SPS. Of the 136 augmentation implants removed, 82% were replaced. The primary reason for implant removal is shown in the table below based on the number of implants removed.

PMA Reason for Implant Removal through 3 Years of Augmentation	N = 136 Implants Removed	
	N	%
Patient Request for Size/Style Change	50	37%
Leakage/Deflation	31	23%
Capsular Contracture	22	16%
Asymmetry/Wrinkling/Sagging/Scarring	22	16%
Infection	7	5%
Hematoma/Seroma	3	2%
Breast Cancer	1	<1%
Total	**136**	**100%**

Table 4b. SPS: Reasons for Implant Removal through 3 Years for Reconstruction - Of the 416 reconstruction patients, there were 97 patients (23.3%) who had 116 implants removed over the three years of follow-up in the SPS. Of the 116 reconstruction implants removed, 60% were replaced. The primary reason for implant removal is shown in the table below based on the number of implants removed.

PMA Reason for Implant Removal through 3 Years of Reconstruction	N = 116 Implants Removed	
	N	%
Capsular Contracture	30	26%
Infection	30	26%
Leakage/Deflation	25	22%
Asymmetry/Wrinkling/Sagging/Scarring	13	11%
Patient Request for Size/Style Change	7	6%
Necrosis/Extrusion	6	5%
Breast Pain	4	3%
Breast Cancer	1	<1%
Total	**116**	**100%**

4. **Adverse Events Risk Rate Following Implant Replacement** - Tables 5a and 5b below show the 3-year cumulative Kaplan-Meier adverse event rates of first occurrence following implant replacement (i.e. revision) on a by implant basis for complications occurring in at least 1% of patients. There were 113 augmentation patients and 70 reconstruction patients who underwent replacement of their implants. For those patients, follow-up data were available on 120 replacement implants in augmentation patients and 76 replaced implants in reconstruction patients.

Table 5a: SPS: 3-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval) Following Augmentation Implant Replacement, by Implant

[illegible]	[illegible]	[illegible]
Reoperation	15.8%	(8.9, 22.3)
Wrinkling	14.6%	(8.0, 21.2)
Implant Removal	12.1%	(5.9, 18.3)
Capsular Contracture III/IV and grade unknown	9.1%	(3.0, 15.1)
Leakage/Deflation	4.4%	(0.0, 8.8)
Asymmetry	3.8%	(0.1, 7.5)
Breast Pain	3.0%	(0.0, 5.5)
Hematoma	1.7%	(0.0, 4.1)
Hypertrophic Scarring	2.0%	(0.0, 4.8)

Table 5b: SPS: 3-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval) Following Reconstruction Implant Replacement, by Implant

[illegible]	[illegible]	[illegible]
Reoperation	30.6%	(18.4, 43.0)
Leakage/Deflation	22.6%	(9.9, 35.3)
Implant Removal	21.1%	(10.6, 31.5)
Capsular Contracture III/IV and grade unknown	18.9%	(8.5, 29.1)
Asymmetry	17.1%	(5.8, 28.3)
Wrinkling	16.0%	(5.0, 27, 0)
Breast Pain	13.1%	(2.9, 23.3)
Infection	4.7%	(0.0, 9.9)
Irritation/Inflammation	3.0%	(0.0, 7.1)
Seroma	3.0%	(0.0, 7.0)
Extrusion	1.9%	(0.0, 5.4)
Hematoma	1.5%	(0.0, 4.5)
Hypertrophic Scarring	1.6%	(0.0, 4.6)
Necrosis	1.4%	(0.0, 4.2)

5. **CTD and Breast Cancer** - Tables 6a and 6b summarize post-implant observations from the SPS pertaining to connective tissue/autoimmune (CTD) disease. These data should be interpreted with caution in that there was no comparison group of similar women without implants. Unconfirmed reports were based on self-reports by the patients. Confirmed reports were based on a diagnosis by a physician. Data pertaining to effects on offspring, mammographic detection of tumors/lesions, lactation problems, and reproduction problems were not collected in these studies. New cases of breast cancer were reported in 2 augmentation patients.

Table 6a. SPS: Reports of CTD through 3 Years for Augmentation, By Patient.

Osteoarthritis/Rheumatoid Arthritis/Unknown	1	19	4.4[a]
Osteoarthritis		1	3.4[b]
Rheumatoid Arthritis	1	3	1.0-1.2[c]
Arthritis (type unknown)		15	-
Ankylosing spondylitis			0.3[d]
Lupus Erythematosus	1		0.2 - 0.5[e]
Total	2	19[f]	

[a]Combined estimates for osteoarthritis and rheumatoid arthritis
[b]Oliveria et al. 1995
[c]Chan et al. 1993; Dugowson et al. 1991
[d]Kaipainen-Seppanen et al. 1997
[e]Uramoto et al. 1999; McCarty et al. 1995
[f]2 aug pts had 2 unconfirmed CTDs

Table 6b. SPS: Reports of CTD through 3 Years for Reconstruction, By Patient.

Osteoarthritis/Rheumatoid Arthritis/Unknown	4	28	4.4[a]
Osteoarthritis	2	8	3.4[b]
Rheumatoid Arthritis		2	1.0-1.2[c]
Arthritis (type unknown)	1	18	-
Ankylosing spondylitis	1		0.3[d]
Lupus Erythematosus			0.2 - 0.5[e]
Total	4	28[f]	

[a]Combined estimates for osteoarthritis and rheumatoid arthritis.
[b]Oliveria et al. 1995
[c]Chan et al. 1993; Dugowson et al. 1991
[d]Kaipainen-Seppanen et al. 1997
[e]Uramoto et al. 1999; McCarty et al. 1995
[f]7 recon pts had 2 unconfirmed CTDs

6. **Subgroup Analyses** - Cox-Regression analyses were performed to identify risk factors for the complications of deflation, capsular contracture (Baker Class III or IV), infection, explantation, and reoperation. Selected significant results of these analyses are summarized below:

   - Deflation was significantly higher with Betadine® surgical pocket irrigation than without. The sponsor analyzed clinical data from their SPS regarding Betadine use and implant deflation. This is the largest study to date with the longest follow-up to examine this issue. For the 1264 augmentation patients (2526 implants), Cox Proportional Hazards Analysis revealed a 3.5-fold elevated risk of implant deflation through 3 years of follow-up associated with Betadine use. This risk of implant deflation with Betadine use was increased by 5.9-fold and 3.6-fold, respectively, for immediate and delayed reconstruction (combined total of 416 patients and 572 implants). Mentor Corporation conducted in-vitro testing of

the integrity of both smooth and textured saline-filled breast implant shells when in contact with Betadine. All implants in contact with Betadine intralumenally for more than 7 days (up to 4 months) exhibited delamination of the implant shell.

- Capsular contracture (Baker Class III or IV) rate was significantly higher in older than in younger patients.

- Capsular contracture (Baker Class III or IV) rates were lower in the inframmary approach in augmentation compared to periareolar.

- There was no difference in capsular contracture (Baker Class III or IV) rate for textured versus smooth implants.

- Spectrum Mammary Prostheses were associated with a higher implant removal and reoperation rate compared to the Saline-Filled Mammary Prostheses.

E. Effectiveness Outcomes for SPS

For augmentation, effectiveness outcomes included breast size change, patient satisfaction, and comfort with appearance. For reconstruction, effectiveness outcomes included breast size change, level of functional living, and depression. These outcomes were reported before implantation and at three years after surgery for those patients who still had at least one of their original implants.

For reconstruction patients, 283 out of the original 416 patients (68%) still had implants and were in the study after three years. Of these 283 patients, the average increase in chest circumference was 1.5 inches.

For augmentation patients, 955 out of the original 1264 patients (76%) still had implants and were in the study after three years. Of these 955 patients, 917 (96%) experienced an increase of at least one cup size at 3 years; the average increase in chest circumference was 2.8 inches. Of the 955 patients still in the study, 860 (90%) indicated being satisfied with the general appearance of their breasts, as measured by the Breast Evaluation Questionnaire (BEQ).

Most augmentation patients who still had their original implants and were still in the study at 3 years exhibited an improvement in the two measured subscales of the Multidimensional Body-Self Relation Questionnaire (MSBRQ) (which measures comfort with your general appearance). For augmentation patients, the Tennessee Self-Concept Scale (which measures self-concept) showed a slight increase at 3 years compared to before implantation.

The Functional Living Index for Cancer (FLIC) (which measures the ability to cope with day-to-day activities), the Depression Inventory (BDI) (which measures the symptoms of depression), and the MSBRQ were collected on reconstruction patients. However, this information was not presented because, without comparative information on similar patients who underwent mastectomy without reconstruction, interpretation of these data are not possible.

XII. SUMMARY OF OTHER CLINICAL INFORMATION

A. SEER Study

Manufacturers of breast implants provided a grant to the Fred Hutchinson Cancer Research Center to perform a study of breast implant failure in a cancer cohort. Cancer patients diagnosed in 1983, 1985, 1987, and 1989 were identified through the Surveillance Epidemiology End Results registry (SEER) from three SEER sites (Iowa, San Francisco/Oakland, and Seattle/Puget Sound). Of the 6563 women identified with early stage cancer and who were less than 65 years of age, and had been treated with mastectomy, 18% (1159) had breast implants. Of the 1159 women who had reconstruction with breast implant(s), there was information on the details of the implant for 1012 women with 1375 implants. The majority of implants were single lumen silicone gel filled implants (40.7%), closely followed by multilumen (double, triple, or quadruple) implants (saline/silicone-gel) (36.7%). Sixteen percent were saline breast implants.

The endpoint for the SEER breast implant study was implant removal. The removal rate for all types of breast implants by Kaplan-Meier was 24% at 5 years and 39% at 10 years (445 of the total 1,375 implants were removed).

Of the 222 saline implants, 96 (43%) were removed by 10 years, which includes implants removed as part of planned reconstruction. Of the 68 saline implants removed for reasons other than planned reconstruction, the most common reason for removal was capsular contracture (24 implants; 35%), followed by mechanical and other (13 implants each, 19%), followed by aesthetic (12 implants; 18%), followed by healing (4 implants; 6%), and followed by malignancy (2 implants; 3%). Mechanical reasons included rupture, leakage, deflation, and injury (accident or puncture). Other reasons included personal preference, non-implant related infection, muscle structure, and chest wall or mastectomy defect/deformity. Aesthetic reasons included implant migration/repositioning, dimpling, asymmetry, contour/size problems.

B. Literature Summary of Potential Systemic Diseases

CTD/Adverse Immunologic Events - Concern over the relationship of silicone breast implants to the development of connective tissue disease such as Scleroderma, Systemic Lupus Erythematosus, rheumatoid arthritis, undifferentiated connective tissue disease, or other autoimmune disease was raised because of case series reporting the occurrence of these diseases in women with implants. In the interim, several epidemiological studies comparing the occurrence of connective tissue disease in women with implants to women without implants have been published in the medical literature. A recent report on the possibility of an association of connective tissue disease and breast implants have concluded that women with silicone breast implants are no more likely to develop connective tissue disease than women without them. The Institute of Medicine (IOM) concluded in 1999 in their report on the safety of silicone that "There is insufficient evidence to support an association of silicone breast implants with defined connective tissue disease." The IOM also stated that "There is no convincing evidence for atypical connective tissue disease or rheumatic disease or a novel constellation of signs and symptoms in women with silicone breast implants. Case reports, of which there are many, do not provide evidence although they may suggest hypotheses that can be tested." [Safety of Silicone Breast Implants. Institute of Medicine National Academy Press, Washington, D.C. 2000. {IOM report}, chapter 8, pp.215-232].

however, found no difference. Another issue of concern during mammography is that the presence of calcification on the implant capsule, either with the implant in place or after the implant is removed if the capsule is left in place, might lead to false positive diagnoses of malignancy.

C. MDR

The Medical Device Reporting (MDR) data below were retrieved from two databases. The Maude database consists of individual manufacturer reports, user facility reports, distributor reports, and voluntary reports. Some of the incidents may have been reported more than once. 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 a distributor. Alternatively, summary reporting was offered to breast implant manufacturers in 1995. Manufacturers can summarize reports of rupture, leaks, deflation/inflation, wrinkling, capsular contracture, and non-specific complaints. Some manufacturers accepted this proposal and send us aggregated data on a quarterly basis.

The MDR summary for Mentor Saline-filled Breast Implants for 1997 through 1999 is as follows:

[illegible]		[illegible] (N=17708)	
Explanted	442 (17%)	Deflations	16,714 (94%)
Surgery	362 (14%)	Capsular Contracture	457 (3%)
Deflations	248 (9%)	Leaks	344 (2%)
Pain	144 (5%)	Wrinkling	172 (1%)
Capsular Contracture	104 (4%)	Non-Specific	21 (0.1%)
Repeat Surgery	79 (3%)		

The overall percentages reported in the table above are calculated as a proportion of the total (N=2634 for Maude and N=17708 for Summary) and do not represent the overall rate of a specific complication. Also, for clarification sake, leaks were reported as "out of box" failures (i.e., no patient contact involved) and non-specific complaints were also non-leaking "out of box" failures.

XIII. PANEL RECOMMENDATION

The General and Plastic Surgery Devices Panel recommended that Mentor's PMA for Saline-Filled and Spectrum® Mammary Prostheses be approved with conditions. The conditions included:

1. Complete and update some of the preclinical mechanical testing, particularly for the new styles and the new materials.
2. Remove from the labeling references to the shaped implants that infer that the implants will improve body contour, because there are no data supplied to support this claim.
3. The labeling should discourage peri-umbilical insertion of the implant.
4. Revision data should continue to be collected post-approval, but there should not be a separate indication for revision.
5. The adverse event data should be reanalyzed and new risk estimate adjustments should be reported that will be more informative to the patient.
6. The panel statistician recommended a further statistical analysis of the data. An important concerned was that the data be fully presented to prospective patients.

however, found no difference. Another issue of concern during mammography is that the presence of calcification on the implant capsule, either with the implant in place or after the implant is removed if the capsule is left in place, might lead to false positive diagnoses of malignancy.

C. MDR

The Medical Device Reporting (MDR) data below were retrieved from two databases. The Maude database consists of individual manufacturer reports, user facility reports, distributor reports, and voluntary reports. Some of the incidents may have been reported more than once. 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 a distributor. Alternatively, summary reporting was offered to breast implant manufacturers in 1995. Manufacturers can summarize reports of rupture, leaks, deflation/inflation, wrinkling, capsular contracture, and non-specific complaints. Some manufacturers accepted this proposal and send us aggregated data on a quarterly basis.

The MDR summary for Mentor Saline-filled Breast Implants for 1997 through 1999 is as follows:

[illegible] (N=2634)		[illegible] (N=17708)	
Explanted	442 (17%)	Deflations	16,714 (94%)
Surgery	362 (14%)	Capsular Contracture	457 (3%)
Deflations	248 (9%)	Leaks	344 (2%)
Pain	144 (5%)	Wrinkling	172 (1%)
Capsular Contracture	104 (4%)	Non-Specific	21 (0.1%)
Repeat Surgery	79 (3%)		

The overall percentages reported in the table above are calculated as a proportion of the total (N=2634 for Maude and N=17708 for Summary) and do not represent the overall rate of a specific complication. Also, for clarification sake, leaks were reported as "out of box" failures (i.e., no patient contact involved) and non-specific complaints were also non-leaking "out of box" failures.

XIII. PANEL RECOMMENDATION

The General and Plastic Surgery Devices Panel recommended that Mentor's PMA for Saline-Filled and Spectrum® Mammary Prostheses be approved with conditions. The conditions included:

1. Complete and update some of the preclinical mechanical testing, particularly for the new styles and the new materials.
2. Remove from the labeling references to the shaped implants that infer that the implants will improve body contour, because there are no data supplied to support this claim.
3. The labeling should discourage peri-umbilical insertion of the implant.
4. Revision data should continue to be collected post-approval, but there should not be a separate indication for revision.
5. The adverse event data should be reanalyzed and new risk estimate adjustments should be reported that will be more informative to the patient.
6. The panel statistician recommended a further statistical analysis of the data. An important concerned was that the data be fully presented to prospective patients.

7. Continued long-term data should be collected with annual reporting to FDA.
8. The Quality of Life data should be reanalyzed and placed on the label in a way that is meaningful to the patient.
9. Assurance that all efforts will be made to fully inform patients of all potential risks.

XIV. CDRH DECISION

FDA concurred with the overall Panel recommendation to approve the PMA. In general, the Panel individual recommendations involved three kinds of concerns: the completion of the mechanical testing, the long-term follow-up of patients, and the availability of a clear and complete description of the risks associated with breast implants for prospective patients. The Panel recommendations regarding risk presentation, quality of life, etc. were addressed in the patient labeling. Long-term follow-up, explant studies, adequacy of patient information, and mechanical testing issues were addressed through the conditions of approval specified in the approval order.

The specific conditions of approval are as follows:

- The first condition of approval requires the collection of patient data for a duration of 10 years. Augmentation and reconstruction patients will be followed even after revision. The results of the study will be included in annual reports.

- The second condition of approval requires a study of explanted devices in order to determine the modes of failure. This should lead to better device designs and, in the long term, to a reduction in the failure rates.

- The third condition of approval, FDA is requiring a focus-group study of the patient informed decision brochure. The study will review content and the format and will suggest ways in which the clarity can be improved. FDA will review the final labeling.

- The fourth condition of approval involves the mechanical endurance of the devices. Fatigue rupture testing of worst case devices and 5-year real-time shelf life testing were required.

The General and Plastic Surgery Devices Panel will meet in the future to review the results of these four conditions of approval.

Inspection of the sponsor's manufacturing facilities was completed on May 10, 2000, and was found to be in compliance with the device Good Manufacturing Practice regulations.

FDA issued an approval order on May 10, 2000.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

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

Postapproval Requirements and Restrictions: See approval order.