SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Saline-Filled Mammary Prosthesis

Device Trade Name: RTV Saline-Filled Mammary Implant

Applicant: McGhan Medical Corporation
700 Ward Drive
Santa Barbara, California 93111

Premarket Approval (PMA) Application Number: P990074

Date of Panel Recommendation: March 2, 2000

Date of Good Manufacturing Practice Inspection: April 8-14, 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:

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

Surgical Practices which will compromise the product's integrity:

- **Adulterated Fill.** Do not place drugs or substances inside the implant other than sterile saline for injection.
- **Alteration.** Do not alter the implant or valve.
- **Do not inject** through the implant shell.
- **Stacking** of implants: Do not place more than one implant per breast pocket.
- Do not allow the implant to come into contact with Betadine®(providone iodine)

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 overexpansion of the device.

2. ***Reuse***
Breast implants are intended for single use only. Do not resterilize.

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 capsulotomy, 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 have 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***
McGhan Medical 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 McGhan Medical implants have not been established. McGhan Medical 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 are irreversible.
- ***Mammography*** - Patients should be instructed to inform their mammographers about the 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.

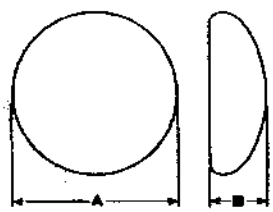
VI. DEVICE DESCRIPTION

The McGhan Medical saline-filled breast implant shells are constructed from RTV (Room Temperature Vulcanized) medical grade silicone elastomer with a PDMS (polydimethlsiloxane) patch positioned on the posterior side. There are smooth and textured (BIOCELL®) surfaced implants with round or BioDIMENSIONAL® shapes. The BIOCELL® texturing covers the entire shell except for the patch area. The minimum shell thickness is 0.014" for the smooth implants and 0.022" for the textured implants. All styles of the implants have anterior diaphragm valves (except for Style 163 which has a posterior diaphragm valve) that allow for filling the implant with sterile saline at the time of surgery via a disposable fill tube.

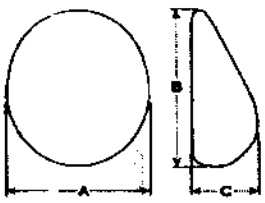
The breast implant styles are as follows:

Style	Surface	Shape	Profile	Size
68	Smooth	Round	Moderate	120-800cc
163	BIOCELL® textured	Shaped	Full Height, Full Projection	360-780cc
168	BIOCELL® textured	Round	Moderate	120-800cc
363	BIOCELL® textured	Shaped	Moderate Height, Full Projection	230-650cc
468	BIOCELL® textured	Shaped	Full Height, Moderate Projection	195-620cc

The following diagrams illustrate the height and projection of an implant.



A = Width; B = Projection
ROUND



A = Width; B = Height; C = Projection
SHAPED

All implants are provided sterile. The implants are sterilized by dry heat. The sterilization method is validated for a sterility assurance level (SAL) of 10^{-6}.

VII. BREAST RECONSTRUCTION ALTERNATIVES

Alternative treatments include, but are not limited to, external implants; autogenous tissue grafts; tissue flaps (e.g., transverse rectus abdominous muscle/TRAM, 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. McGhan Medical began marketing the RTV saline-filled mammary prostheses, which are the subject of this PMA, in 1988. A total of 704,802 devices were sold during the period 1988 though 1999 in over 50 countries. McGhan 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 on this issue suggests that the information is insufficient to draw definitive conclusions.

X. SUMMARY OF PRECLINICAL STUDIES

The pre-clinical studies are divided into three sections: chemistry, toxicology, and mechanical.

A. Chemistry Data

1. **Materials** - The silicone shell is manufactured by the reaction of linear silanol end-blocked polydimethylsiloxanes with a stoichiometric excess of methyltriacetoxysilane. An organic tin compound was used as a catalyst. The vulcanization is conducted at room temperature (RTV). Treated amorphous silica is included in the formulation with the linear dimethylsiloxane polymer to reinforce the toughness of the subsequent elastomer.

   In case of valve construction, it is fabricated from polydimethylsiloxane elastomers that are molded into valve components. The patch material consists of a laminate of a thin (0.005 inch) vulcanized elastomer sheet, laminated with a thicker (0.020 inch) unvulcanized elastomer. The patch material sheeting is cut into shape, placed onto the appropriate position on the shell, and heated (vulcanized) to cause the unvulcanized material to cure to a crosslinked elastomer that is covalently bonded to the shell. The function of the thin (0.005 inch) vulcanized elastomer sheet is to prevent the thicker (0.020 inch) unvulcanized elastomer from sticking to the opposing inside surface of the shell during vulcanization.

2. **Extent of Crosslinking** - The amounts of extractables from different lots of the implants were reported. It was concluded that the crosslinking is similar among the different lots because comparable amounts of extractables are obtained from them.

   The amount of extractables is inversely related to degree of crosslinking. The amount of extractables is determined by extensively extracting the shell material with n-hexane and the residuals are measured as a fraction (Sol Fraction, W_S) of the total sample weight. The number of crosslinks (γ_C) per average molecule is determined using the formula: $\gamma_C = 1/(W_S + W_S^{1/2})$.

   The Sol Fraction obtained for the subject device was 2.6 weight percent residue. Therefore, the calculated degree of crosslinking (γ_C) is 5.3 crosslinked units per number-average molecule.

2. **Chemical Analyses of Low Molecular Weight Components Present in the Device** Finished sterilized devices were used for the analysis of extractables. The following table gives the amounts of various low molecular weight components present in the subject device. The techniques used to detect these components include solvent extraction followed by gas chromatography-mass spectrometry, and gel permeable chromatography. Complete metal analyses were provided. Only a few metals of importance (metals that are known to be toxic) are listed in the table. Infrared spectroscopy studies were performed to provide evidence that there is no qualitative chemical difference between the surface and bulk of silicone materials. Surface silica analysis provided no evidence of free silica presence on the shell. Separate chemical analyses on the shell and valve (Leaf Valve) were provided. The chemical analyses performed on extractable residues obtained by extraction of whole device with both hexane and ethanol showed similar quantities of cyclic PDMS. The only difference was that the hexane extract contained both the linear and cyclic PDMS whereas the ethanol extracted residue contained only the cyclic PDMS. The following table lists

the concentration of various cyclic PDMS detected and quantitated from hexane extract. The lower cyclic PDMS (up to D_8) could not be detected on gc-ms analysis of extractables obtained from the whole device. Cyclic PDMS from $D_9 - D_{48}$ were detected and analyzed. In the following table, only some of the cyclic PDMS are listed that were detected in the hexane extract. Either the whole device or the shell part was used in the hexane extraction process.

Concentrations of Low Molecular Weight Components Detected

Identification	Molecular Weight	Solvent (100 ppm)
D3	222 amu	0.6 ppm*
D4	296 amu	0.9 ppm*
D5	370 amu	2.1 ppm*
D6	444 amu	5 ppm*
D7	518 amu	3.1 ppm*
D8	592 amu	3.4 ppm*
D9	666 amu	11.3 ppm
D10	740 amu	36.7 ppm
D11	814 amu	70.0 ppm
D12	888 amu	135.1 ppm
D13	962 amu	206.7 ppm
MeSiloxane	unknown	0.9 ppm*
D14	1,036 amu	309.1 ppm
D15	1,110 amu	407.2 ppm
D16	1,184 amu	475.2 ppm
D17	1,258 amu	521.0 ppm
D18	1,332 amu	524.1 ppm
D19	1,406 amu	513.9 ppm
D20	1,480 amu	478.0 ppm
Isopropanol	60.09 amu	0.71 ppm*
D25	1,850 amu	358.5 ppm
D30	2,220 amu	285.3
D35	2,590 amu	241.2 ppm
D40	2,960 amu	200.5 ppm
D45	3,330 amu	160.5 ppm
D48	3,552 amu	159.1 ppm
Acetic Acid	60.50 amu	Not reported
Toluene	92.13 amu	Not reported
Xylenes	106.2 amu	5.69 ppm*
1,1,1 Trichloroethane	133.4 amu	Not reported
Hexamethyl Disilazane	161 amu	Not reported
Methyl Triacetoxy Silane	222 amu	Not reported
Polybiphenyls	mixture	Not detected*
Tin	118.7 amu	50-100 ppm
Platinum	195.09 amu	Not detected at sensitivity level -3 ppm
Arsenic	74.9 amu	Not detected at sensitivity level - 100 ppm
Lead	207.2 amu	Not detected at sensitivity level - 10 ppm
Manganese	54.93 amu	Not detected at sensitivity level - 1 ppm
Zinc	65.37 amu	Not detected at sensitivity level - 30 ppm
Phosphorus	30.97 amu	Not detected at sensitivity level - 300 ppm
Total Extraxtables (hexane extract)	mixture	2.5%

D3 – D48 represent cyclic polydimethyl siloxanes (PDMS).
amu = atomic mass units (Daltons)
* analysis provided on shell only

B. Toxicology Data

1. **Pharmacokinetics** - Literature articles on pharmacokinetic studies done on Dow Corning silicone gel were based on the assumption that the silicone gel represents the "worst" case scenario as both the silicone shell and silicone gel are made of similar silicone polymer precursors. The sponsor also provided the concentrations of leachable cyclic oligomeric dimethylsiloxanes for the shell and gel. Though the concentrations of some of the cyclic oligomers are similar, the other oligomer concentrations differ. The total amount of leachable small cyclic oligomeric siloxanes is so small that toxicological concerns are minimized as supported by the literature. No new pharmacological studies need to be conducted.

   The worst case dose for the cyclic oligomer D_4 (if all of D4 present in the elastomeric shell was released at once) would be 7 mg/device. The total amount of D_4 under a worst case situation from two implants in a 60 kg woman would be 14 mg/60 kg or 0.233 mg/kg. The "no effect levels" for D_4 (from literature) are 42 mg/kg (reproductive effect), 12 mg/kg (liver enlargement effect), and 2000 mg/kg (LD50). As the margins of safety are 180, 52, and 8,583 for reproductive, liver enlargement and LD_{50} respectively, even the worst case scenario concentrations of D4 do not warrant pharmacokinetic studies on the shell.

2. **Cytotoxicity** - The device (Styles 64 and 168 including valve and overlay assembly) was eluted with minimum essential medium (MEM) and the eluant was used to test for the cytotoxic effect on mouse fibroblast cells (L-929). The eluant was found to be not cytotoxic.

3. **Irritation** - Saline and cotton seed oil extracts of representative Styles 64 and 168, which include smooth shell, textured shell, leaf valve, diaphragm valve, and patch/overlay assembly, were used to evaluate intracutaneous toxicity (irritation) in rabbits. There was no evidence of significant irritation or toxicity.

4. **Implantation** – A 90-day muscle implantation with histology study was conducted in New Zealand White rabbits with smooth RTV shell, textured RTV shell, Leaf Valve, Diaphragm Valve and Plug Assembly, and Patch Overlay Assembly separately. The results showed that none of the materials was toxic.

   Additionally, each component was implanted separately in a subchronic toxicity study. Two grams of each component was implanted in female Fisher 344 rats (90 days, subcutaneously) in a pulvarized form to maximize the surface area exposure of the implanted materials. Animals were evaluated for mortality, body weight, clinical chemistry, hematology, organ weights, organ/body weight ratios, organ/brain weight ratios, and tissue pathology. The results indicated that the subject device did not produce any subchronic toxicity in rats.

5. **Acute Systemic Toxicity** - Both saline and cottonseed oil extracts of the final device (smooth and textured RTV shell with valve and patch/overlay assembly) were injected either intravenously or intraperitoneally into mice to evaluate the systemic acute toxicity at 4, 24, 48, and 72 hours. The representative smooth and textured shells (Styles 64 and 168) were tested separately. There was no mortality or evidence of significant systemic toxicity from the extracts.

6. **Hemocompatibility** - Whole rabbit blood was added to the test article (smooth and textured RTV shell with valve and patch/overlay assembly) in saline for 1 hour at 37°C and the resulting solution was examined spectroscopically for cell lysis. The smooth and textured shells (Styles 64 and 168) were tested separately. The results showed that the device was non-hemolytic.

7. **Pyrogenicity** - The saline extract of both the smooth and textured shells with valve and overlay assembly, when injected intravenously via the marginal ear vein of rabbits, did not produce any pyrogenic effect. The smooth and textured shells were tested separately.

8. **Immunotoxicity** - The immunotoxicity of the shell, leaf valve, diaphragm valve, and the patch overlay assembly were separately studied by subcutaneous implantation in female B6C3F1 mice. In addition, two device styles were evaluated for delayed contact sensitization in the guinea pig.

   - RTV Shell - Among the immunologic parameters evaluated were: spleen and thymus weights, thymus histopathology, hematological measurements, spleen IgM antibody response to the T-dependent antigen, T cell and T cell subsets B cell enumeration, mixed leukocyte response to allogenic spleen cells, and natural killer (NK) cell activity. The slight changes seen between the test article and the control were not considered biologically significant.

   - Valve - Both the leaf valve and the diaphragm valve were separately studied. The immunologic parameters evaluated were: spleen and thymus weights, thymus histopathology, hematological measurements, spleen IgM antibody response to the T-dependent antigen, T cell and T cell subsets and B cell enumeration, mixed leukocyte response to allogeneic spleen cells, and natural killer (NK) cell activity. The results showed that the valve assembly did not adversely affect the immune system.

   - Patch and Overlay Assembly - The immunologic parameters evaluated were: spleen and thymus weights, thymus histopathology, hematological measurements, spleen IgM antibody response to the T-dependent antigen, T cell and T cell subsets and B cell enumeration, mixed leukocyte response to allogenic spleen cells, and natural killer (NK) cell activity. Only the NK cell assay demonstrated a statistically significant dose related increase in the implanted groups when compared to a sham control. However, the increase in the mean was not significant by the Dunnett's Test.

   - Sensitization - Saline and cottonseed oil extracts of the device (smooth and textured RTV shell with valve and patch/overlay assembly) were used to evaluate the sensitization potential in guinea pigs by Magnusson and Kligman method. The smooth and textured shells (Styles 64 and 168) were tested separately. The results showed that the subject device was not a sensitizer.

9. **Bacterial Mutagenicity** - Two device styles (Style 64 and Style 168) consisting of all components were studied. Saline and DMSO extracts of the device were used to study bacterial mutagenicity on Salmonella bacterial cells in presence and absence of metabolic activator. The device was found not to be a bacterial mutagen.

10. **Mammalian Cell Mutagenicity** - Saline and DMSO extracts of the subject device (Styles 64 and 168 with all components) were used to study mammalian cell mutagenicity on Mouse Lymphoma L5178Y/TK+/- cells in the presence and absence of metabolic activator. Results indicated that the device was not a mutagen.

11. **Unscheduled DNA Synthesis Assay (rat primary hepatocytes assay)** - Saline and DMSO extracts of the device (Styles 64 and 168 with all components) were used to study the DNA damage with rat primary hepatocytes in the presence and absence of metabolic activator. The device was found to be non-mutagenic and non-genotoxic.

12. **Embryonic Cell Transformation Assay (Mouse 3T3 Cell Assay)** - Saline and DMSO extracts of the device (Styles 64 and 168 with all components) were used for the Cell Transformation Assays. BALB/3T3 Mouse Embryo Cells when subjected to the transformation assay in the presence of metabolic activation did not show any transformation potential of the device.

13. **Carcinogenicity**
    - RTV Silicone Elastomer Shell - Female Fisher rats were subcutaneously implanted with either pulverized Low Density Polyethylene (LDP) as control or RTV Silicone Elastomer (RTV) as test article. The third group of animals served as sham control. The LDP and RTV were administered in gelatin capsules. Both the pulverized LDP and pulverized RTV elicited a response of fibrous encapsulation of the material with extension of fibrosis into septa penetrating between the fragments of LDP and RTV. The implant site lesions were similar in both LDP and RTV control groups. No evidence of systemic toxicity as measured by body weights, hematology, serum chemistry, and organ weight was seen. Sixty-five (65) fibrosarcomas occurred at the implant site in LDP group and 68 in RTV control group. No fibrosarcomas occurred in sham controls. Several other neoplastic and non-neoplastic responses were observed in several organs and tissues in all three groups of animals. These changes were of the type commonly observed in Fisher 344 rats and, therefore, not related to the implanted materials.

    - Valves and Patch - Pulverized Diaphragm Valve, Leaf Valve, Plug Assembly, Overlay Assembly, Patch and Overlay Assembly were subcutaneously implantated in female Fisher 344 rats. An additional group of Fisher 344 rats served as sham control animals. Fibrosarcomas were observed in both test article and control implantation sites, which are typical for rodents when implanted with solid state objects. There was no systemic toxicity observed.

14. **Reproductive Toxicology** - The sponsor did not conduct any reproductive toxicology studies on the device. Instead, the sponsor submitted summaries on the reproductive and developmental studies on silicone elastomer, low molecular weight silicones, silicone fluid, and silicone gel. All these articles were published in peer-reviewed journals. These literature articles indicate that the silicone materials are not toxic.

15. **Teratology** – Styles 64 and 168 with all other components were pulverized and subcutneously implanted in female Sprague-Dawley rats. There were no statistically significant differences in the C-section parameters evaluated. The silicone materials used in this experiment did not produce teratologic effects.

C. Mechanical Data

1. **Tensile Strength and Ultimate Elongation** – Tensile-breaking strength and ultimate elongation testing were performed in accordance with ASTM F703 and D412. Dumbbell-shaped samples were taken from finished, sterilized devices. The sample dimensions were 4.5" in length and 0.25" from the thinnest width at mid-section. The average sample thickness ranged from 0.019" to 0.024". The smallest, medium and largest sizes were tested; however, the results were pooled across size because all size because all shells are constructed of the same material and are of similar thickness. The average tensile strength for all samples was above 1000 psi. All samples met the ASTM F703 criteria of 350% for ultimate elongation. The results were:

68	95	1456	678
163	90	1039	571
168	90	1088	572
363	90	1026	578
468	90	1054	572

2. **Tear Resistance** - Testing was performed in accordance with ASTM D624. Dumbbell-shaped samples (cut from Die B version) were taken from finished, sterilized devices. The smallest, medium and largest sizes were tested; however, the results were pooled across size because all size because all shells are constructed of the same material and are of similar thickness. The specimens were 4.3" in length and 0.4" thinnest width at mid-section. The average sample thickness ranged from 0.012 to 0.025". A 0.02" nick was made at the mid-section. The results were:

68	95	100.3
163	90	108.6
168	90	106.6
363	90	104.2
468	90	129.7

3. **Adhered Joint** - Testing was performed in accordance with ASTM F703. Samples were taken from finished, sterilized devices. The die used was dependent on the joint involved. 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 met the ASTM F703 criteria of 2.5 lbs for breaking force. The results were:

68	95	Diaphragm valve/shell	6.08
		Patch/shell	4.80
163	90	Diaphragm valve/shell	7.39
		Patch/shell	5.40
168	90	Diaphragm valve/shell	11.30
		Patch/shell	5.93
363	90	Diaphragm valve/shell	7.17
		Patch/shell	5.16
468	90	Diaphragm valve/shell	7.72
		Patch/shell	5.09

For the valve/shell joints, the primary modes of failure were valve delamination and shell breakage at joint. For the patch/shell joints, the primary modes of failure were shell tear and breakage.

4. **Valve Competency** - Two valve competency tests were performed. Both tests were performed in accordance with ASTM F703, but with a modified protocol. The samples were taken from finished, sterilized devices.

For the first valve competency test, 60 samples each of the Styles 68 (smooth/diaphragm) and 168 (textured /diaphragm) were tested. The prepared sample was subjected to a pressure of 126cm H_2O, held for 5 minutes, and then visually checked for signs of leakage. The pressure was released and then held at 30cm H_2O for 5 minutes and then check for leakage. Then pressure was released and then held at 3cm H_2O for 5 minutes and then checked for leakage. If no leakage was visually detected, then the sample passed. All samples passed. The intraluminal pressure within a saline breast implant is considered to be as high as 126 cm H_2O when the patient is lying on the implant.

For the second valve competency test, 20 samples each of the Styles 68 and 168 were tested. The prepared sample was subjected to increasing pressure at a rate of 1 to 1.5 psi/sec until failure occurred or until reaching a maximum pressure of 90psi (6328 cm H_2O). The results for this second valve competency test were:

68	20	14.0
168	20	15.4

All samples failed by valve delamination. For those that slipped prior to failure, the pressure recorded at slippage was assigned as the failure pressure. The minimum intraluminal pressure obtained at failure in this testing was 872 cmH_2O, which is estimated to be a minimum factor of safety of 6.9 times that of *in vivo* intraluminal pressure of 126 cm H_2O.

5. **Static Rupture** – Two tests were performed: ultimate blow and ultimate burst testing.

Ultimate blow testing assesses the force to failure due to a single compression of an implant between two plates. This test was performed on 3 samples of each style with a target of 85% compression to create the failure. The measured forces at failure were:

68	120	1758
163	360	3473
168	120	1843
363	230	2403
468	195	2577

Ultimate burst testing assesses the resistance of implants to rupture from excessive fill volumes. This testing represents the percentage of the recommended fill volume that can be attained in an inflatable implant before failure. The minimum acceptable fill before failure established for this test was 600% of the maximum recommended fill volume. A total of 100 devices were selected for testing. Ten samples were taken from both the smallest and largest sizes of Styles 68, 163, 168, 363 and 468 standard production implants. All tested samples exceeded the minimum specification of 600% maximum fill volume.

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 percent compression fatigue testing in distance/strain control on Styles 68, 168, 163, 363, and 468. For this testing, the implants were tested at various % compression values (e.g., 50%, 60%, 70%) until failure or 1M cycles was reached. Based on % compression data, a correlation of compression and applied load was developed to generate AF/N curves. While there were actual measured loads at some of the % compression values at 1M and 10M cycles, a large portion of the load data was extrapolated. The endurance load level for this testing ranged from 11 to 23 lbs.

As stated above, this testing was not considered worst case testing. 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:

Style	Surface	Size	Thickness
68	Smooth	120cc	0.014"
168	BIOCELL® Textured	120cc	0.022"

As a condition of approval, the sponsor provided a protocol for new fatigue rupture testing. The worst case styles defined above will be tested using shells obtained through standard production. The fatigue rupture testing will begin as soon as the final protocol is reviewed.

7. **Shelf-Life** – 4-year, real-time aged shelf life testing was performed on 12 samples of Style 168. Physical testing included patch shell leakage, valve competence, fused adhered joint, ultimate break force, ultimate elongation, and tear force. Package integrity testing included sterility (limited, 2 samples) and peel force. This testing did not include microbial challenge or dye penetration testing. However, using the shelf-life data in conjunction with their clinical data that demonstrated no exaggerated deflation rates. The current 4-year shelf life will remain on the label with the condition of approval that (1) McGhan Medical immediately perform microbial challenge and dye penetration testing on their implants that have undergone shipping and handling and (2) complete their 5-year real-time shelf life testing. This 5-year real-time shelf-life testing is already underway.

XI. SUMMARY OF THE PROSPECTIVE CLINICAL STUDIES

A. Study Designs

The safety and effectiveness of McGhan Medical Saline-Filled Breast Implants were evaluated in four open label, multi-center clinical studies: the 1990 Augmentation/Reconstruction Study, the Large Simple Trial (LST), the 1995 Augmentation Study (A95), and the 1995 Reconstruction Study (R95). Because the 1990 study utilized devices and surgical practices that are not current, these data are not reported below.

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 0-4 weeks and at 12 months.

A95 study was an open label, prospective study of patients aged 18 years or older seeking saline-filled breast implants for augmentation purposes (i.e., unilateral or bilateral breast hypoplasia, breast ptosis, post-lactational mammary involution, congenital breast deformity) with adequate tissue available to cover the implant, who did not have a CTD (connective tissue disease) as determined by a questionnaire, and who agreed to the study conditions. Patients with advanced fibrocystic disease considered pre-malignant without mastectomy, existing carcinoma of the breast without mastectomy, previous history of breast augmentation or reconstruction, inadequate/unsuitable tissue (e.g., h/o compromised vascularity, h/o compromised wound healing), ptotic breasts with nipple below infra-mammary fold without concurrent mastopexy, active infection, pregnant/nursing, high risk medical conditions (e.g., obesity, diabetes, chronic lung disease, severe CV disease), use of drugs (e.g., anticoagulants) which might increase surgical risk, and patients with inappropriate psychological characteristics (e.g., inappropriate attitude or motivation) were excluded from the study.

R95 study design, follow-up intervals, study endpoints, and device styles were the same as A95. The only major difference was the patient population with respect to inclusion criteria. Patients with unilateral or bilateral mastectomy for cancer or for prophylactic mastectomy with either immediate or delayed reconstruction were enrolled. Patients who already had a tissue expander placed and were now ready for implants were included to increase enrollment. In addition, breast cancer information such as use of chemotherapy, radiation, or hormonal therapy was collected at baseline.

Follow-up visits in the 1995 studies occurred pre-operatively and post-operatively at 0-4 weeks, 6 months, and at 1, 2, 3, 4, and 5 years; these studies are currently ongoing. Safety assessments in the 1995 studies consisted of adverse event rates and rates of additional surgical treatment. Effectiveness assessments in the 1995 studies consisted of patient satisfaction, breast size change (augmentation patients only), and measures of body esteem/self esteem/body image.

B. Patient Accounting and Baseline Demographic Profile

The LST Study enrolled 2,333 augmentation patients, 225 reconstruction patients, and 317 revision patients with an overall one-year follow-up compliance rate of 62 %. The 1995 Augmentation Study enrolled 901 augmentation patients by 92 investigators at 64 sites with a three-year follow-up compliance rate of 76%. The 1995 Reconstruction Study enrolled 237 patients by 51 investigators at 42 sites with a three-year follow-up compliance rate of 71%. Across the three studies, there were 14 deaths, all of which were unrelated to the implant or the implant surgery.

Demographic information obtained from the 1995 studies revealed that nearly 90% of both augmentation and reconstruction patients were Caucasian, and more than half of study participants were married. The median age of the augmentation patients was 32 years (range: 19-66); for reconstruction patients the median age was 47 years (range: 25-77).

With respect to surgical baseline factors in the 1995 studies, for augmentation patients, the most frequently used devices were textured round, the most common incision sites were periareolar and inframammary, and the most frequent placement of the implant was submuscular. For reconstruction patients, the most frequently used devices were textured BioDIMENSIONAL, the most common incision site was the mastectomy scar, and the most frequent placement of the implant was submuscular.

C. Safety Outcomes of LST

The cumulative Kaplan-Meier risk of first occurrence of adverse events (and 95% confidence interval) is shown in Table 1 based on indication.

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

Capsular Contracture III/IV	7.2	(5.8, 8.6)	12.5	(7.3, 17.8)	11.8	(7.1, 16.4)
Leakage/Deflation	3.6	(2.6, 4.5)	2.6	(0.0, 5.2)	5.4	(2.0, 8.8)
Infection	1.5	(0.9, 2.1)	6.2	(2.9, 9.5)	3.3	(1.1, 5.6)
Implant Removal	6.1	(4.9, 7.3)	13.7	(8.7, 18.6)	7.8	(4.2, 11.5)

D. Safety Outcomes of 1995 Studies

Safety outcomes assessed in the 1995 Studies are reported in Tables 2-6. Complications following implant removal with replacement (i.e., revision) are not included in Tables 2-4 or in Table 6.

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. A95/R95: Three-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient and By Implant.

Additional Surgical Procedures	21.1%	(18.4, 23.8)	16.2%	(14.5, 17.9)	38.7%	(32.3, 45.0)	33.4%	(28.1, 38.7)
Breast Pain*	15.6%	(13.2, 17.9)	12.2%	(10.6, 13.7)	15.3%	(10.3, 20.2)	11.5%	(7.7, 15.2)
Wrinkling*	10.5%	(8.4, 12.6)	9.7%	(8.2, 11.1)	23.3%	(17.5, 29.1)	21.9%	(17.0, 26.9)
Asymmetry*	10.1%	(8.1, 12.1)	n/a**	n/a**	33.0%	(26.6, 39.4)	n/a**	n/a**
Nipple Paresthesia*	9.3%	(7.4, 11.2)	7.9%	(6.6, 9.2)	<1	<1	<1	<1
Implant Palpability/Visibility*	9.2%	(7.2, 11.1)	8.0%	(6.7, 9.3)	20.0%	(14.5, 25.5)	18.0%	(13.4, 22.6)
Capsular Contracture III/IV	8.7%	(6.8, 10.6)	6.1%	(5.0, 7.3)	25.3%	(19.5, 31.2)	22.2%	(17.4, 27.0)
Loss of Nipple Sensation*	8.4%	(6.5, 10.2)	6.3%	(5.2, 7.5)	12.0%	(7.4, 16.6)	12.9%	(8.8, 17.0)
Implant Malposition*	8.2%	(6.3, 10.0)	5.5%	(4.4, 6.6)	12.2%	(7.8, 16.6)	9.5%	(6.1, 12.9)
Implant Removal for Any Reason	7.6%	(5.8, 9.4)	6.2%	(5.1, 7.3)	22.5%	(17.1, 28.0)	18.2%	(13.8, 22.5)
Skin Paresthesia*	7.2%	(5.5, 9.0)	5.7%	(4.6, 6.8)	5.6%	(2.5, 8.6)	5.4%	(2.7, 8.0)
Scarring Complications	6.4%	(4.8, 8.0)	5.1%	(4.0, 6.1)	6.0%	(2.7, 9.2)	5.3%	(2.6, 8.0)
Leakage/Deflation	5.0%	(3.5, 6.4)	2.7%	(1.9, 3.4)	6.2%	(2.9, 9.5)	4.6%	(2.2, 7.1)
Irritation/Inflammation*	2.9%	(1.8, 4.0)	2.4%	(1.7, 3.1)	6.6%	(3.3, 9.8)	5.6%	(3.0, 8.1)
Seroma	2.6%	(1.6, 3.7)	1.6%	(1.0, 2.2)	3.9%	(1.4, 6.4)	3.3%	(1.3, 5.3)
Hematoma	1.6%	(0.7, 2.4)	<1	<1	1.3%	(0.0, 2.8)	<1	<1
Skin Rash	1.6%	(0.8, 2.4)	1.6%	(1.0, 2.2)	3.3%	(0.9, 5.7)	2.5%	(0.7, 4.3)
Capsule Calcification*	1.2%	(0.4, 1.9)	<1	<1	4.7%	(1.9, 7.6)	4.3%	(1.9, 6.7)
Infection	<1	<1	<1	<1	4.8%	(2.0, 7.5)	3.9%	(1.7, 6.1)
Delayed Wound Healing*	<1	<1	<1	<1	2.7%	(0.6, 4.9)	2.0%	(0.4, 3.6)
Implant Extrusion	<1	<1	<1	<1	2.6%	(0.6, 4.7)	2.3%	(0.6, 4.0)
Tissue/Skin Necrosis	<1	<1	<1	<1	3.6%	(1.1, 6.0)	2.7%	(0.8, 4.5)

*These complications were assessed with severity ratings. Only the rates for moderate, severe, or very severe (excludes mild and very mild ratings) are shown.

**Not applicable

2. **Types of Additional Surgical Procedures Through 4 Years** - Of the 901 augmentation patients in the A95 Study, there were 204 (22.6%) who had at least one additional surgical procedure over the 4 years of follow-up. A total of 402 additional procedures were performed in A95 over 4 years. Of the 237 reconstruction patients in the R95 Study, there were 95 (40.1%) who had at least one additional surgical procedure, excluding additional planned procedures such as nipple reconstruction and nipple tattoo procedures. A total of 151 additional procedures were performed in R95 over 4 years. Table 3 shows the types of additional surgical procedures performed over 4 years in the 1995 Studies based on the total number of additional procedures.

Table 3. A95/R95: Types of Additional Surgical Procedures Through 4 Years

Implant Removal w/Replacement	122	30%	45	30%
Capsule Related[1]	78	19%	18	12%
Add/Remove Saline	45	11%	8	5%
Aspiration	28	7%	7	5%
Mastopexy	28	7%	0	0%
Scar Revision/Wound Repair	33	8%	20	13%
Reposition Implant	19	5%	6	4%
Biopsy/Lump Removal	16	4%	7	5%
Other Secondary Surgical Treatment	16	4%	19	13%
Implant Removal w/o Replacement	10	3%	17	11%
Removal of Skin Lesion or Cyst	6	2%	1	1%
Nipple-Related Procedure[2]	1	0%	3	2%
Total	**402**	**100%**	**151**	**100%**

[1]Capsule related includes capsulectomy, capsulotomy, and capsulorraphy.
[2]These nipple procedures were not planned nipple reconstructions or nipple tattoos.

3. **Reasons for Implant Removal Through 4 Years** - Of the 901 augmentation patients in A95, there were 81 patients (9.0%) who had 132 implants removed over 4 years. Of the 237 reconstruction patients in R95, there were 58 patients (24.5%) who had 62 implants removed through 4 years. Of the 132 augmentation implants removed, 92.4% were replaced; of the 62 reconstruction implants removed, 72.6% were replaced. The primary reason for implant removal is shown in Table 4 below based on the total number of implants removed.

Table 4. A95/R95: Reasons for Implant Removal Through 4 Years

Patient Request for Change Size/Style	56	43%	14	23%
Leakage/Deflation[1]	56	42%	19	31%
Capsular Contracture	8	6%	13	21%
Wrinkling/Asymmetry/Malposition	6	5%	6	10%
Breast Pain	3	2%	0	0%
Iatrogenic Injury	1	1%	0	0%
Infection	1	1%	6	10%
Implant Extrusion	1	1%	4	7%
Total	**132**	**100%**	**62**	**100%**

Notes: [1]Includes unreported/unknown.

4. **Adverse Events Risk Rate Following Implant Replacement** - Tables 5a and 5b show the 2-year cumulative Kaplan-Meier adverse event risk rates of first occurrence following implant replacement (i.e., revision) on a by implant basis. There were 69 augmentation patients (108 implants) and 37 reconstruction patients (40 implants) in the 1995 Studies who had their implants removed and replaced and who were followed after implant replacement.

Table 5a: A95/R95: Two-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval) Following Augmentation Implant Replacement, by Implant

Leakage/Deflation	9.1%	(3.4, 14.7)
Capsule Contracture III/IV	7.3%	(1.5, 13)
Implant Removal	5.4%	(0.2, 10.5)
Infection	1.0%	(0.0, 3.0)

Table 5b: A95/R95: 2-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval) Following Reconstruction Implant Replacement, by Implant

Capsule Contracture III/IV	47.7%	(31.0, 64.5)
Implant Removal	25.5%	(9.8, 41.3)
Infection	7.3%	(0.0, 17.3)
Leakage/Deflation	5.3%	(0.0, 12.5)

5. **CTD and Breast Disease** - Tables 6a and 6b summarize post-implant observations from the 1995 Augmentation and 1995 Reconstruction Studies pertaining to connective tissue/autoimmune disease (CTD) and breast disease (including breast carcinoma). 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 and mammographic detection of tumors/lesions were not collected in these studies.

Table 6a. A95/R95: Reports of CTD Through 4 Years, By Patient.

Graves' Disease	2	1	0	0
Hyperthyroiditis	1	0	2	0
Inflammatory Bowel Disease	0	0	0	1
Lupus Erythematosus and/or Rheumatoid Arthritis	0	0	3	1
Thyroiditis	0	0	2	2
Chronic Fatigue Syndrome or Fibromyalagia	2	0	0	0
Total	5	1	7	4

Table 6b. A95/R95: Reports of Breast Disease Through 4 Years, By Patient.

Benign	44	4.9%	11	4.6%
Malignant	1	0.1%	19	8.0%
Unknown Outcome	9	1.0%	1	0.4%

6. **Other** – McGhan Medical conducted an analysis of the A95 data for leakage/deflation and did not find statistically significant higher leakage/deflation with Betadine® use; however, leakage/deflation was numerically higher with Betadine use. The lack of statistical significance noted by McGhan Medical could be due to the small sample size of the subgroup, as their study was not designed to address this issue.

E. Effectiveness Outcomes for 1995 Studies

Effectiveness was assessed by bra cup size change (augmentation patients only), patient satisfaction, body image, body esteem, and self concept. These outcomes were assessed before implantation and at three years after surgery for patients with both original and replacement saline devices, except for bra size, which was measured within the first year and a half after surgery. Patients who had their implants removed without replacement of study devices were not included in effectiveness assessments.

For augmentation patients, 858 out of the original 901 patients (95%) still had implants and were in the study within 18 months after the surgery. Of these 858 patients, 330 (38.5%) increased by one cup size and 418 (48.7%) increased by two cup sizes. 31 (3.6%) did not increase their cup size.

For augmentation patients, 689 out of the original 901 patients (76%) still had implants and were in the study after three years. 655 of these 689 patients (95%) indicated being satisfied with their breast implant surgery.

The 689 augmentation patients after three years scored higher (better) than the general U.S. female population before implantation on the SF-36 and MOS-20, which measure general health related quality of life. After 3 years, augmentation patients had a worsening of their SF-36 and MOS-20 scores. The Tennessee Self-Concept Scale (which measures overall self-concept) showed no change over the 3 years. The Rosenberg Self Esteem Scale (which measures overall self-esteem) showed a slight improvement over the 3 years. The Body Esteem Scale (which measures overall self-esteem related specifically to one's body) showed no change over the 3 years. The Semantic Differential Scale (which measures attitudes about your breasts compared to attitudes about yourself) showed an increased positive attitude towards breasts compared to self.

For reconstruction patients, 169 out of the original 237 patients (71%) still had implants and were in the study after three years. 149 of these 169 patients (88%) indicated being satisfied with their breast implant surgery. The SF-36, MOS-20, The Tennessee Self-Concept Scale, The Rosenberg Self Esteem Scale, Body Esteem Scale, and Semantic Differential Scale data 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. Since McGhan Medical Saline-filled Breast Implants were introduced after 1988, it is likely that none were involved in this study.

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 the occurrence of case series reporting the occurrence of these diseases in women with implants. Several epidemiologic studies comparing the occurrence of connective tissue disease in women with implants to women without 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].

Cancer - Concern over cancer arose with the publication of a paper indicating that the injection of silicone fluid into the peritoneal cavity of susceptible mice would result in the development of plasmocytomas, a type of immune system (B cell) cancer. The parallel disease in humans is called multiple myeloma. The IOM reviewed all current studies on the relationship of silicone implants to cancer in 1999 and concluded that "There is a consistent, substantial, long-term base of scientific evidence bearing on the experimental carcinogenicity and clinical breast or other cancer experience with silicone and silicone breast implants. Based on its review of this evidence, the committee concludes that the available evidence does not support an association of silicone or silicone breast implants with experimental carcinogenesis (other than rodent solid-state carcinogenesis), primary or recurrent breast cancer, breast sarcoma or other solid tumors, lymphoma, or myeloma." [IOM report chapter 9, pages 233-241]

Implants, Breast Feeding, and Effects on Children - There are two issues that have been raised about breast implants and breast-feeding. First, is the quality of breast milk changed by breast implants and second, is it more difficult to feed an infant with an implanted breast? Although there are no current methods for detecting *silicone* in breast milk, there has been a study in which *silicon* levels have been measured in breast milk of women with implants, women without implants, cows milk, and commercially available infant formula. Much higher levels of silicon were found in the infant formula and cow's milk than in the milk of nursing mothers with breast implants for augmentation. There were no differences in the level of silicon in nursing women with breast implants compared to those women without. The IOM report on breast implants stated that the committee found convincing evidence that infants breast-fed by mothers with silicone gel breast implants receive no higher silicon intakes from breast milk than infants breast-fed by mothers without breast implants. However, the IOM also noted that several studies have indicated that many women with breast implants may not be able to breast feed their babies because of lactational insufficiency. In one study cited in the IOM report, up to 64% of women with breast implants were unable to successfully breast feed their infants due to lactational insufficiency as compared to less than 10% of women without breast implants.

Some women with breast implants have reported health problems in their breast-fed children. However, studies have not provided evidence that illnesses observed in children of mothers with breast implants were related to breast implants. The IOM has concluded that evidence for an association of maternal silicone breast implants and children's health effects is insufficient or flawed.

Studies on the reproductive and teratogenic effects of silicone, that is their ability to cause birth defects in the offspring of mothers or fathers exposed to various forms of silicone, have not indicated that silicone has either toxic reproductive or teratogenic effects in experimental animals. [IOM Report, chapter 4, pp.80-113; chapter 11, pp.248-263]

Interference with Mammography and Capsular Calcification - Silicone implants may interfere with standard mammography because they are radio-opaque, that is, the radiation is blocked by the implant. Subglandular implants have been observed to obscure from 15-100% of the breast tissue and submuscular implants somewhat less. While the issue of implants interfering with visualization to some degree is clear, it is not clear whether this may result in a delay in the detection of cancer. In some studies cited by the IOM, women with implants had larger primary tumors, more positive axillary nodes, or a lower percentage of palpable tumors visible on mammography than women without implants. Others 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, it might lead to false positive diagnoses of malignancy or false negatives.

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 incidences 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, an 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 on McGhan saline-filled breast implants for 1997 through 1999 is as follows:

Explanted	306 (18%)	Deflations	9022 (80%)
Surgery	141 (8%)	Capsular Contracture	1647 (15%)
Repeat Surgery	97 (6%)	Non-Specific	264 (2%)
Infection	91 (5%)	Leaks	166 (1%)
Capsular Contracture	72 (4%)	Wrinkling	142 (1%)

XIII. PANEL RECOMMENDATION

The General and Plastic Surgery Devices Panel recommended approval of the PMA subject to the following conditions:

1. Data only support indications of augmentation and reconstruction.
2. Labeling be modified to account for lack of data on anatomical design.
3. Perform long-term follow-up with focus on censoring.
4. Revise the risk characterization.
5. Perform analyses on censoring and Quality of Life.
6. Rectify CTD discrepancies.
7. Perform mechanical testing on thinnest wall (worst case). Sponsor to work with FDA to develop appropriate fatigue and fold flaw methodology.
8. Develop SOPs for explanted devices.

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: completion of the mechanical testing, long-term follow-up of patients, and availability of a clear and complete description of the risks associated with breast implants for prospective patients. The Panel recommendations regarding indications for use, risk characterization, quality of life, and connective tissue disease 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 April 14, 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.