Summary of Safety & Effectiveness Data (SSED)
Updated draft in 9/1/03 email

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Gel-Filled Mammary Prosthesis

Device Trade Name: McGhan BIOCELL® Textured and Smooth Silicone-Filled Breast Implants

Applicant: Inamed Corporation
5540 Ekwill Street
Santa Barbara, California 93111

Premarket Approval (PMA) Application Number: TBD

Date of Panel Recommendation: *TBD*
Date of Good Manufacturing Practice Inspections: March 19 - 21, 2003 and June 9 - 12, 2003
Date of Notice of Approval to Applicant: *TBD*

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 disease of the breast without adequate treatment.
- **Pregnant or Nursing.** Augmentation in women who are currently pregnant or nursing.

Surgical Practices that could compromise the product's integrity:

- **Alteration.** Do not alter the implant.
- **Stacking of implants.** Do not place more than one implant per breast pocket.

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.

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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. ***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.

V. PRECAUTIONS

1. ***Specific Populations***
   Safety and 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 a 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***
   Inamed 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 Silicone-Filled Breast Implants have not

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been established. Inamed 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 lifetime devices and they will likely undergo implant removal, with or without replacement, over the course of their life.
   - ***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.

VI. DEVICE DESCRIPTION

The McGhan Silicone-Filled Breast Implant shells are constructed from medical grade silicone elastomer with a patch positioned on the posterior side. The implants have shells made from a single or double lumen. There are round smooth and round or shaped textured (BIOCELL®) surface implants. The BIOCELL® texturing covers the entire shell except for the patch area. The minimum shell thickness is for the smooth implants and for the textured implants.

The breast implant styles are as follows:

Style No.	Surface Texture	Shape	Profile	Sizes (cc)
10	Smooth	Round	Moderate Projection	120-800cc
20	Smooth	Round	Full Projection	120-800cc
40	Smooth	Round	Standard (Moderate) Projection	80-560cc
45	Smooth	Round	Full Projection	120-800cc
110	BIOCELL® Textured	Round	Moderate Projection	90-510cc
120	BIOCELL® Textured	Round	Full Projection	180-650cc

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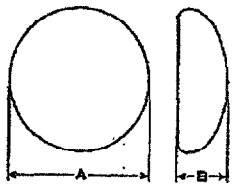
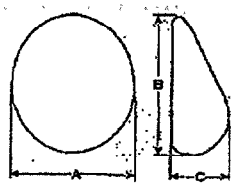
Style No.	Surface Texture	Shape	Profile	Sizes (cc)
153	BIOCELL® Textured	Shaped	Full Height, Full Projection	360-720cc

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



A = Width & Height; 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 abdominus muscle/TRAM, latissimus dorsi muscle, gluteal muscle), or no treatment. An alternative treatment may also be to receive saline-filled implants.

VIII. MARKETING HISTORY

Silicone-filled breast implants are preamendment devices that have been used since 1963. In 1975, Inamed began marketing gel-filled mammary prostheses. On July 9, 1991, Inamed submitted PMA P910044 in response to the final rule published in the Federal Register on April 10, 1991 (56 FR 14620), requiring manufacturers of gel-filled breast implants to submit PMAs within 90 days.

On January 6, 1992, the FDA called for a moratorium on the use of silicone gel-filled breast implants until new safety information could be reviewed by an advisory panel. Inamed complied with the moratorium.

On February 20, 1992, the General and Plastic Surgery Devices Advisory Panel recommended that breast implants be made available only on a limited basis under carefully controlled clinical studies. After a careful evaluation of the public health need, the alternatives to silicone gel-filled breast implants, and the known, potential, and suspected risks, the FDA Commissioner adopted the Panel's recommendation on April 16, 1992, and FDA lifted the voluntary moratorium. Subsequent to the

lifting of the moratorium, Inamed elected to discontinue the manufacture and sale of gel-filled breast implants in the United States.

As part of the Advisory Panel ruling, and based on public health need, on April 16, 1992 FDA indicated that silicone gel-filled breast implants could continue to be available for women seeking breast reconstruction in a study identified as an "Adjunct Study". On March 30, 1998, Inamed received approval for the McGhan Adjunct Study (PMA P910044/A24) and the manufacture and sale of McGhan Silicone-Filled Breast Implants was reinstituted in the United States.

IX. POTENTIAL ADVERSE EFFECTS

The following is a list of potential adverse events that may occur with any breast implant surgery. The risks include: implant rupture/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), 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.

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X. SUMMARY OF PRECLINICAL STUDIES

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

A. Chemistry Data

1. Materials

The device is composed of silicone gel encased in a silicone elastomer envelope (shell). The shell contains a patch, made from silicone elastomer, which covers the hole in the shell that results when the shell is removed from the mold during manufacture. During manufacture, the gel is injected through the patch and the fill hole is sealed using a small amount of silicone adhesive.

The gel is manufactured from a formulation that is approximately by weight silicone polymer with some chemically reactive molecules along the polymer chain. When heated, the reactive components on the polymer combine to form a crosslinked three dimensional network. This reaction is catalyzed by the addition of a platinum-silicone complex present in ppm quantities. The gel contains approximately by weight polydimethylsiloxane polymer devoid of chemically reactive components, that is extractable using powerful organic solvents such as hexane. This polymer swells the crosslinked network to provide the gel with the consistency to mimic soft tissue.

The device shell is manufactured using two different elastomers. Both elastomers are categorized as two-part platinum cure elastomers. These elastomers utilize a mixture of high molecular weight vinyl containing siloxane polymer, a low molecular weight methylhydrogen containing siloxane crosslinker, a volatile organic compound that serves as a reaction inhibitor and a platinum-silicone complex catalyst. When heated, the polymer chains react to form a crosslinked three-dimensional network. The elastomer is reinforced with treated amorphous fumed silica to enhance toughness. The shell consists of an inner and outer layer sandwiched around a "*barrier layer*" designed to impede the diffusion of components of the gel through the shell. All layers of the shell are produced using a copolymer of siloxane. The barrier layer differs from the base layer in that it contains a higher percentage of in the copolymer.

The patch is manufactured from two types of silicone elastomer. The inner layer of the patch is a two-part platinum cure elastomer similar to the shell material, except the polymer is siloxane copolymer. The outer layer of the patch is a peroxide cure silicone elastomer. The adhesive used to seal the fill hole in the patch is

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2. **Extent of Crosslinking**

Shell and Patch Materials - The physical strength (tensile strength) and elasticity (elongation at failure) of the shell and patch materials is a result of the extent of crosslinking achieved during the vulcanization process. The physical properties of cured samples of all elastomer lots used for breast implant shells and patches are measured to ensure they meet or exceed pre-established material specifications prior to being released for use in the manufacture.

The results of this testing ensure the conformity of crosslink density across lots of implant shell and patch materials. In addition, the physical properties of the device shell, for three material lots under a variety of processing conditions, were measured during process validation testing. This testing ensures not only the consistency in the extent of crosslinking across material lots, but also ensures that the process used by Inamed to produce the implant shell is adequate to achieve a crosslink density that assures the strength and elasticity of the implant shell meets or exceeds specifications. This testing demonstrated the extent of crosslinking of the elastomers used in the device shell is sufficient to assure all shells meet a specification of a minimum lb break force and elongation.

Gel Materials - Every lot of gel received by Inamed is tested to ensure the crosslink density conforms to predetermined specifications, using penetrometer testing, prior to being released for use in the manufacture of breast implants. In addition, every batch of mixed gel is penetrometer tested to ensure the crosslink density conforms to predetermined specifications.

The penetrometer testing on mixed gel lots occurs during the manufacture of every lot of McGhan Silicone-Filled Breast Implants produced by Inamed. Penetrometer samples are obtained from the same batch as is used to fill the implants and are cured along with the implants in the same oven. The uniformity of the crosslink density across all lots of gel used in McGhan Silicone-Filled Breast Implants is thus ensured by this testing performed on each and every breast implant lot produced. All lots of gel used in Inamed's McGhan Silicone-Filled Breast Implants have an extent of crosslinking sufficient to achieve a penetrometer reading of mm.

3. **Chemical Analyses of Low Molecular Weight Components Present in the Device**

Finished sterilized devices were analyzed for extractables. In addition, virgin shells, which had been patched and sterilized, but not yet gel filled, were also extracted to provide information about the interaction between the gel and the shell materials. 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, using both a mass spectrometer (GC-MS) and a flame ionization detector (GC-FID), and by gel permeation chromatography. Complete metal analyses were provided. Only a

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few metals of importance are listed in Table 2. Separate chemical analyses on the shell (including patch) and the gel are provided.

The highest level of extracts was isolated using hexane as the extracting solvent. Everything detected in the extracts using the polar solvent (isopropanol), was also detected in the extracts using the non-polar solvent (hexane). Table 1 also lists the concentration of the various oligomers quantified from hexane extract. PDMS from $D_9 - D_{21}$ were detected and analyzed from extracts of both the shell and gel. L_9 to L_{18} were detected in hexane extracts of the gel and shell that had been exposed to gel. The presence of siloxanes in the gel-exposed shell, which were not present in the virgin shell, indicates that components of the gel dissolve into the shell. Gravimetric analysis indicates that the gel dissolves in the shell at approximately by weight of the shell. In addition, containing siloxane components were found in the hexane extracts of the shell and gel. These siloxanes are present in the shell as a result of the process used to produce the polymer used in the shell elastomer formula. The presence of small amounts of siloxane components in the gel indicates that in the shell migrate into the gel, since no containing polymers are used in the gel formulation.

Concentrations of Low Molecular Weight Components Detected (in ppm by component weight)

Identification	Molecular Weight (amu)	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
D3	222	ND<146	ND<17	ND<7
D4	296	ND<69	ND<8	ND<3
D5	370	ND<6	ND<1	ND<1
D6	444	ND<6	ND<1	ND<1
D7	518	ND<6	ND<1	ND<1
D8	592	ND<8	ND<1	ND<1
D9	666	ND<8	6	ND<1
D10	740	ND<8	12	2
D11	814	11	21	9
D12	888	32	94	26
D13	962	64	62	65
D14	1036	237	186	209
D15	1110	366	278	285
D16	1184	491	351	317
D17	1258	593	432	328
D18	1332	729	527	342
D19	1406	678	601	0
D20	1480	735	605	212
D21	1554	668	474	129

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Concentrations of Low Molecular Weight Components Detected (in ppm by component weight) (continued)

Identification	Molecular Weight (amu)	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
L1	236	ND<63	ND<7	ND<3
L2	310	ND<8	ND<1	ND<1
L3	384	ND<8	ND<1	ND<1
L4	458	ND<10	ND<1	ND<1
L5	532	ND<8	ND<1	ND<1
L6	606	ND<7	ND<1	ND<1
L7	680	ND<8	2	4
L8	754	ND<8	2	ND<1
L9	828	ND<9	8	ND<1
L10	902	19	17	ND<1
L11	976	35	29	ND<1
L12	1050	63	49	ND<1
L13	1124	103	84	ND<1
L14	1198	132	108	ND<1
L15	1272	169	128	ND<1
L16	1346	183	106	ND<1
L17	1420	161	137	ND<1
L18	1494	177	128	ND<1
siloxanes	mixed	242	985	2762

Concentrations of Metal Contents Detected (in ppm)

Metal	Molecular Weight (amu)	Shell (Inner and Outer Layers)	Shell (Barrier Layer)	Patch	Gel
Antimony	121.76	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Arsenic	74.92	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Barium	137.33	1	1	2	1
Beryllium	9.01	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Cadmium	112.41	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Calcium	40.08	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Chromium	52.00	0.3	0.4	1.8	0.2
Cobalt	58.93	ND (<0.2)	ND (<0.2)	ND (<0.2)	ND (<0.2)
Copper	63.55	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)

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Concentrations of Metal Contents Detected (in ppm) (continued)

Metal	Molecular Weight (amu)	Shell (Inner and Outer Layers)	Shell (Barrier Layer)	Patch	Gel
Iron	55.84	ND (<0.1)	0.2	8.7	1.2
Lead	207.19	ND (<0.2)	ND (<0.2)	ND (<0.2)	0.3
Magnesium	24.30	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Manganese	54.94	ND (<0.05)	ND (<0.05)	0.15	ND (<0.05)
Mercury	200.59	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Molybdenum	95.94	ND (<0.5)	ND (<0.5)	ND (<0.5)	ND (<0.5)
Nickel	58.69	ND (<0.2)	1	0.7	ND (<0.2)
Potassium	39.10	ND (<1)	8	1	ND (<1)
Selenium	78.96	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Silver	107.87	ND (<0.1)	0.2	ND (<0.1)	ND (<0.1)
Sodium	22.99	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Thallium	204.38	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Vanadium	50.94	ND (<0.4)	ND (<0.4)	ND (<0.4)	ND (<0.4)
Zinc	63.40	0.12	ND (<0.05)	3.9	0.22

Concentrations of Catalyst Metals Detected (in ppm by component weight)

Identification	Molecular Weight (amu)	PQL	Implant Shell (ppm)	Patch (ppm)	Gel (ppm)
Tin	118.71	0.01	0.05	6.60	0.06
Platinum	195.08	0.01	3.30	2.60	4.00

In House Report 104-659, which accompanied a 1997 appropriations bill, Congress asked the U.S. Department of Health and Human Services (DHHS) to sponsor a study of the safety of silicone breast implants by the Institute of Medicine (IOM) of the National Academy of Sciences. In 2000, the Institute of Medicine released a report on the Safety of Silicone Breast Implants. This report was compiled by the Committee on the Safety of Silicone Breast Implants, from the Division of Health Promotion and Disease Prevention. In general, the committee concluded "that a review of the toxicology studies of silicones known to be used in breast implants does not provide a basis for concern at expected exposures." The committee also indicated that "evidence is lacking for an association between platinum in silicone breast implants and local or systemic health effects in women who have these implants."

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B. Toxicology Data

1. Pharmacokinetics

A literature discussion was provided regarding the pharmacokinetics of silicone elastomers, gel, fluids, and low molecular weight compounds. The reviewed literature included published journal articles and publicly available Dow Corning studies. The literature indicated that silicone materials appear to have low mobility, typically remaining where implanted, eliciting only a local response.

In addition, a pharmacokinetics study of silicone gel was performed. The study design consisted of three female rats that were subcutaneously implanted with approximately 3.4 grams of carbon 14 radiolabeled silicone gel for 30 days. After dosing, rats were housed in individual glass metabolism chambers, which allowed separate collection of carbon dioxide, potential expired volatiles, feces and urine. Blood was drawn throughout the study period. Low amounts of the radiolabel were collected in blood (0.0190% of dose), or were measured cumulatively in expired air (0.0004% of dose), feces (0.0186% of dose) and urine (0.0005% of dose). In regard to individual tissues, the liver, muscle and skin had the highest counts (0.0122, 0.0055 and 0.0020% of dose, respectively). The vast majority of the gel remained at the implantation site (~100% of dose), thus demonstrating that the gel was encapsulated, with minimal movement away from the site of implantation.

2. Cytotoxicity

Minimum essential medium (MEM) extracts of test articles representative of elastomer and gel materials used in gel-filled devices were evaluated for cytotoxic effects on mouse fibroblast cells (L929). The results showed that the test articles were noncytotoxic.

3. Irritation

Saline, sesame seed oil, polyethylene glycol (PEG), and alcohol in saline (1:10) extracts of test articles representative of elastomer and gel materials used in gel-filled devices were evaluated for intracutaneous toxicity (irritation) in rabbits. The results showed that the test articles were not irritants.

4. Acute Systemic Toxicity

Saline, sesame seed oil, PEG, and alcohol in saline (1:10) extracts of test articles representative of elastomer and gel materials used in gel-filled devices were evaluated for systemic toxicity in mice. There was no animal mortality. The results showed that the test articles were not toxic.

5. Hemocompatibility

Whole rabbit blood in saline was exposed for 1 hour at 37°C to test articles representative of elastomer and gel materials used in gel-filled devices. The blood and saline mixture was

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examined spectroscopically for cell lysis. The results showed that the test articles were non-hemolytic.

6. **Pyrogenicity**
Saline eluate of test articles representative of elastomer and gel materials used in gel-filled devices was injected intravenously via the marginal ear vein of rabbits. The temperature of the animals was monitored. The eluate did not produce a fever response. The results showed that the test articles were non-pyrogenic.

7. **Immunology**
Test articles representative of elastomer and gel materials used in gel-filled devices were evaluated for immmotoxicity and dermal sensitization.

- Immunotoxicity – Mice were subcutaneously implanted with test articles and evaluated by standard immunological methodology. The parameters included: 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.

  Exposure to the implant shell did not affect the immunological functions of the study animals. Although there was a statistically significant increase in the antibody-forming response observed between groups in the study, this was considered related to the historically low response of the control group, as compared to an actual change in activity due to test article exposure. In the gel evaluation, there were no statistically significant differences between the test article and control groups for the immunologic assays.

  Although not considered functionally relevant, there were statistically significant numeric differences associated with the cell-typing assay when the patch test article was compared to the control. For another patch related elastomeric test article, there were some statistical differences between the middle dose and control groups. As these differences were not also observed for the high dose group, the findings were not considered biologically relevant. For the test article containing RTV adhesive, the height and therefore, surface area and volume of the implant were substantially greater than the other implanted materials. Subsequently, at the time of implantation to accommodate the test article, the skin was stretched tightly in the surgical area and the incision sites did not fully close, which delayed healing. In this RTV adhesive study, there were statistically significant differences between the test article and control groups for the natural killer cell assay. Since natural killer cell activity can be affected by cytokines and cytokines are released in association with normal healing, the natural killer cell assay results may have reflected the delayed healing

associated with the implant sites. Overall, the data indicate that the test articles did not adversely affect the immune system.

- Sensitization - Saline and sesame seed oil extracts of the test articles were used to evaluate the sensitization potential in guinea pigs by the Magnusson and Kligman method. The results showed that the test articles were not sensitizers.

8. Mutagenicity

Test articles representative of elastomer and gel materials used in gel-filled devices were evaluated for mutagenicity using several standard assays.

- Bacterial Mutagenicity (Ames Test) - Saline, ethanol, and/or DMSO extracts of elastomer and gel test articles were evaluated for bacterial mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic.

- CHO/HGPRT Forward Mutation Assay – Ethanol extracts of elastomer and gel test articles were evaluated for mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic.

- *In Vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in CHO Cells - Ethanol extracts of elastomer and gel test articles were evaluated for mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic.

  - Mouse Lymphoma Mutagenicity Assay - Saline and DMSO extracts of an elastomer test article were evaluated for mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic.

  - Unscheduled DNA Synthesis Assay - Saline and DMSO extracts of an elastomer test article were evaluated for mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic.

  - Cell Transformation Assay – Saline and DMSO extracts of an elastomer test article were evaluated for mutagenicity in the presence and absence of metabolic activation. The results showed that the test articles were not mutagenic. In addition, cell transformation assays were performed by Dow Corning using culture media and ethanol extracts of silicone gel. The results showed that the gel test article was not mutagenic.

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9. Muscle Implantation

Test articles representative of elastomer and gel materials used in gel-filled devices were evaluated in 90-day muscle implantation studies that were conducted in New Zealand White rabbits. Test article implantation sites were macroscopically and histologically assessed, as compared to a low-density polyethylene control. The gross observations were classified as either non-reactive or slightly reactive, and the microscopic observations were given an overall toxicity rating of zero for each test article. The results showed that the test articles were non-toxic. Additional implantation testing was also performed, as is discussed below under the subchronic and chronic toxicity/carcinogenicity sections. The findings of all studies were that the test articles did not elicit a toxic response.

10. Subchronic Toxicity

Test articles representative of elastomers used in gel-filled devices were evaluated in a 90-day subchronic toxicity study. Female Fischer 344 rats were evaluated for mortality, body weight, clinical chemistry, hematology, organ weights, organ/body weight or brain weight ratios, and tissue histopathology. The histopathological findings at the implant site were those typically associated with the implantation of test article and included fibrous encapsulation. The histological findings in non-implant site tissues were considered typical for the animals at their age and occurred in similar incidences and severity among the control and implanted groups.

The results demonstrated that the test articles did not produce subchronic toxicity in rats. Silicone gel was evaluated in a 6-week subchronic toxicity study in female Fischer 344 rats that primarily focused upon the histology of the implantation sites. The gel was encapsulated with connective tissue, without evidence of a granulomatous inflammatory reaction. In response to gel, the connective tissue septea surrounded but did not penetrate the gel. The physiologic response to the pulverized low-density polyethylene control consisted of connective tissue septea that penetrated between separate pulverized particles. Additionally, long-term exposure periods were incorporated into the toxicity assessment of the chronic toxicity/carcinogenicity testing. The results showed that the test articles were non-toxic.

11. Chronic Toxicity and Carcinogenicity

Test articles representative of elastomer and gel materials used in gel-filled devices were subcutaneously implanted in female Fisher 344 rats. The elastomers were pulverized prior to implantation. No evidence of systemic toxicity or carcinogenicity, other than solid state tumorigenicity, was observed in association with the test articles. The incidence and type of histologic findings other than those related to the presence of a foreign body reaction were typical of Fischer 344 rats and were not considered test article related. Encapsulation of pulverized low-density polyethylene control or elastomer test article varied somewhat from that of the gel due to their differing physical characteristics. Whereas the connective tissue septea penetrated between separate pulverized polyethylene or elastomeric particles,

the connective tissue septea surrounded but did not penetrate the gel. As previously stated, solid state tumorgenicity was observed in the studies. This is a typical finding for this type of study, as it is a known rodent-specific response to the implantation of materials.

12. Reproductive Toxicology

A literature discussion was provided regarding reproductive and developmental toxicity studies on silicone elastomers, gel, fluids, and low molecular weight compounds. The reviewed literature included published journal articles and publicly available Dow Corning studies. The literature indicated that the silicone materials are neither reproductive nor developmental toxins.

In addition, an "extended F_1-generation" evaluation was performed by Inamed. In that evaluation, F_1-generation rats were exposed to the test article *in utero*. Female F_1-generation animals were also implanted with the test article. The resulting mating indices demonstrated that the F_1-generation animals in both the test article and the sham control groups were capable of successful breeding and subsequent birthing of live pups. Furthermore, there were no significant histological differences observed between the test article and sham control groups with respect to the reproductive organs of male and female F_1-generation rats.

13. Developmental Toxicity (Teratology)

Silicone gel was subcutaneously implanted in female Sprague-Dawley rats. The animals were exposed to either 0.62, 7.28 or 14.70 g/kg test article. There were no biologically significant differences observed between the controls and the implanted groups for the maternal dam and fetal pup parameters evaluated, including pregnancy rates, dam organ weights, and fetal survival, weight, sex and morphological development. The results showed that the gel did not produce developmental effects.

In addition, test articles representative of elastomer materials used in gel-filled devices, were pulverized and subcutaneously implanted with 2 g/kg test article in female Sprague-Dawley rats. Again, there were no biologically significant differences observed between the controls and implanted groups for the maternal dam and fetal pup parameters evaluated, including pregnancy rates and fetal survival, weight, sex and morphological development. The results demonstrated that the test articles did not produce teratologic effects.

C. Physical/Mechanical Data

1. Static Rupture

Ultimate blow testing assesses the force to failure due to a single compression of an implant. Standard production Style 40 and Style 110 implants, representative of Inamed

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

gel-filled devices, were tested. The testing was performed based on worst case device testing. The following styles were identified as being worst case:

Style	Surface	Size (cc)	Thickness (in)
40	Smooth	80	0.013
110	BIOCELL® Textured	90	0.018

This testing was performed on three devices of each Style (40 and 110), using a 5,000 lb load cell. The measured average forces at failure were:

Style	Size (cc)	Avg. Force (lbf)
40	80	1,245
110	90	1,861

It is expected that the load used for this testing is much greater that what would be experienced *in vivo*.

2. **Fatigue Rupture**

Fatigue rupture testing assesses the number of cycles at specific applied loads that a device can endure without rupture, until a rupture occurs. Standard production Style 40 and Style 110 implants, representative of Inamed gel-filled devices, were tested. The testing was performed based on worst case device testing. The following styles were identified as being worst case:

Style	Surface	Size (cc)	Thickness (in)
40	Smooth	80	0.013
110	BIOCELL® Textured	90	0.018

The testing was conducted with equipment capable of applied load control. For this testing, three implants of each Style (40 and 110), were tested at each applied load level (20, 30, 40, and 55 lbs), until failure or 6.5 million cycles was reached. The runout results are provided in the following table.

Style	Size (cc)	Force (lbs)	Minimum # of Cycles (millions)
40	80	55	6.5
110	90	30	6.5

Applied load averages were calculated for all applied load test cycles and AF/N curves were generated. The threshold force, below which an implant can undergo an unlimited number of cycles without failure, was determined for Style 40 implants to be 55 lbs applied force

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

and 30 lbs applied force for Style 110 devices. It is expected that these loads are much greater than what would be experienced *in vivo*.

3. **Gel Bleed**
Gel bleed testing assessed the diffusion rates of silicone gel through the shell. Standard production Style 40 and Style 110 implants, representative of Inamed gel-filled devices, were tested. The study design was consistent with ASTM F703 and involved the use of the silicone disk methodology. The normalized weight gain values obtained from devices over the 8 week course of the study were 0.0152g/cm^2 for smooth surface devices and 0.0048 g/cm^2 for textured surface devices.

4. **Gel Cohesivity**
Gel cohesivity and penetration testing assess the cohesive and cure characteristics of silicone gel, respectively. For the gel cohesivity study, data from the evaluation of gel-filled devices associated with Final Product Release Testing (FPRT) were obtained. The study design was consistent with ASTM F703, specifically the gel pendent section. The gel cohesion values were well below the 4.5 cm maximum identified in ASTM F703 and ranged from for 31 FPRT lots, which comprised a total of 112 packaging lots. For the gel penetration study, the penetration data was collected during standard production and consisted of the data from 112 gel assembly lots. The penetration values ranged from penetrometer units.

5. **Shelf Life**
A five year accelerated shelf life study was performed on the largest sizes of McGhan Style 45 (smooth round) and Style 153 (textured shaped) silicone-filled implants. These devices were representative of the Style 10, 20, 40, 45, 110, 120 and 153 product lines. Prior to aging and testing, all samples were subjected to a shipping simulation in accordance with ASTM D4169.

Mechanical testing of the implants included testing for shell ultimate break force, shell ultimate elongation, shell tensile set, patch joint integrity, and gel cohesion. Additionally, Style 153 implants were also tested for bladder joint integrity, since they were the only models with that design.

Packaging testing included visual inspection, thermoform peel force and dye penetration. Dye penetration testing was performed in accordance with ASTM F1929. ASTM F1929 has gone through consensus review and voting and has been validated through round-robin testing procedures for repeatability and reproducibility.

Based on the results of the accelerated shelf life testing, there is no statistically significant decrease in physical properties after five years of accelerated aging. Therefore, this testing supports a five year expiration date for McGhan Style 10, 20, 40, 45, 110, 120 and 153 silicone gel-filled implants.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

XI. SUMMARY OF THE PROSPECTIVE CLINICAL STUDIES

A. Study Designs

The safety and effectiveness of McGhan Silicone-Filled Breast Implants were evaluated in three multi-center clinical studies: the 1990 McGhan Medical Corporation Mammary Implant Study, the McGhan Medical Corporation Silicone-Filled Breast Implant Core Clinical Study (Core), and the McGhan Medical Corporation Silicone-Filled Breast Implant Adjunct Clinical Study (Adjunct). Because the 1990 Study utilized devices and surgical practices that are not current, those data are not reported below.

The Adjunct Study was designed as a prospective 5-year open enrollment study to assess safety outcomes for a large number of patients. Patients are those seeking breast reconstruction or revision of an existing implant for medical reasons. Patients must have adequate tissue available to cover the implant and be willing to follow study requirements, and saline implants must be deemed unsuitable for medical reasons such as thin skin. Patients are excluded from the study for the following reasons: currently pregnant or nursing, advanced fibrocystic disease considered premalignant without subcutaneous mastectomy, existing carcinoma of the breast without mastectomy, abscess or infection in the body at time of enrollment, any disease including uncontrolled diabetes known to impact wound healing, tissue characteristics incompatible with mammaplasty (e.g., tissue damage from radiation, compromised vascularity or ulceration), any condition that may constitute an unwarranted surgical risk, inappropriate psychological characteristics, and unwillingness to undergo further surgery for revision if medically required. Follow-up visits occur post-operatively at 1, 3, and 5 years. Safety assessments consist of complication rates and rates of reoperation. Patient enrollment and follow-up in the Adjunct Study is currently ongoing.

The Core Study was designed as a prospective study of patients aged 18 years or older seeking silicone-filled breast implants for augmentation (i.e., unilateral or bilateral breast hypoplasia, breast ptosis, asymmetry, aplasia), reconstruction (i.e., mastectomy for cancer or breast trauma, prophylactic mastectomy, and contralateral asymmetry for the unaffected breast), or revision of an existing implant. Patients must have had adequate tissue available to cover the implant and be willing to follow study requirements. The exclusion criteria for patients in the Core Study were identical to those in the Adjunct Study.

Patients' medical history including breast disease and breast cancer information were collected at baseline. Follow-up visits occur post-operatively at 0-4 weeks, 6 months, and annually through 10 years. Serial MRI to detect silent rupture of the implant for a subset of patients occurs subsequent to the annual follow-up visits at 1, 3, 5, 7, and 9 years post-implant. Safety assessments consist of complication rates and rates of reoperation. Additionally, post-implant reports of connective tissue disease and breast disease were obtained. Effectiveness assessments consist of patient satisfaction, breast size change (augmentation patients only), and measures of patient quality of life. Patient follow-up in the Core Study is currently ongoing.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

B. Patient Accounting and Baseline Demographic Profile

The Adjunct Study enrolled 15,465 reconstruction patients and 9,881 revision patients through 1,272 Investigators at 2,355 sites as of the data extract for this report, with new patient enrollment ongoing. Of those reconstruction patients who have reached a scheduled follow-up visit time point, 5,537 (53.8%) returned for their 1 year visit and 670 (27.0%) returned for their 3 year visit. For revision patients, 3,180 (43.9%) returned for their 1-year visit and 460 (19.9%) returned for their 3-year visit. There were 68 patient deaths in the Adjunct Study, all of which were unrelated to the implants or the implant surgery.

The Core Study enrolled 494 augmentation patients, 221 reconstruction patients, and 225 revision patients through 33 investigators at 46 sites. All patients have reached the 2-year scheduled follow-up visit time point, with a compliance rate of 90% for the augmentation patients, 95% for the reconstruction patients, and 87% for the revision patients. There were 12 patient deaths in the Core Study, all of which were unrelated to the implants or the implant surgery.

Demographic information obtained from the Adjunct Study revealed that approximately 60% of participants were married, more than 40% were employed in professional occupations, and more than 70% had at least some college education. The median patient age was 44 years for both reconstruction and revision patients.

Demographic information obtained from the Core Study revealed that over 80% of patients were Caucasian and most study participants were married (49% of augmentation patients, 75% of reconstruction patients, and 64% of revision patients). Approximately half were employed in professional occupations and more than three fourths had at least some college education. The median patient age was 34 years for augmentation patients, 50 years for reconstruction patients, and 44 years for revision patients.

With respect to surgical baseline factors in the Adjunct Study, for both reconstruction and revision patients, the most frequently used devices were round with a fairly equal distribution of smooth and textured surface.

With respect to surgical baseline factors in the Core Study, for augmentation patients, the most frequently used devices were round, with a smooth surface somewhat more common than textured. The most common incision sites were inframammary and periareolar, and the most frequent placement of the implant was submuscular. For reconstruction patients, the most frequently used devices were shaped with a textured surface, the most common incision site was the mastectomy scar, and the most frequent placement of the implant was submuscular. For revision patients, the most frequently used devices were round, and the textured surface (round and shaped) was more common than smooth. The most common incision site was inframammary, and the most frequent placement of the implant was submuscular.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

C. Safety Outcomes for Adjunct Study

The cumulative Kaplan-Meier risk of first occurrence of complications (and 95% confidence interval) is shown in the table provided below, based on indication.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Adjunct: 3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant

Complication	Reconstruction				Revision			
	By Patient (N = 15,465)		By Implant (N = 26,935)		By Patient (N = 9,881)		By Implant (N = 19,099)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
Reoperation	44.1%	(42.0%, 46.2%)	37.2%	(35.5%, 38.8%)	34.5%	(31.9%, 37.0%)	28.1%	(26.3%, 29.9%)
Implant Replacement /Removal	28.2%	(26.1%, 30.3%)	21.9%	(20.3%, 23.5%)	24.1%	(21.7%, 26.5%)	19.5%	(17.8%, 21.1%)
Capsular Contracture	17.6%	(15.7%, 19.4%)	12.7%	(11.5%, 14.0%)	20.0%	(17.6%, 22.3%)	15.2%	(13.6%, 16.8%)
Asymmetry	16.3%	(14.4%, 18.2%)	N/A		9.8%	(7.9%, 11.6%)	N/A	
Implant Palpability/ Visibility	11.8%	(10.2%, 13.4%)	9.4%	(8.3%, 10.6%)	13.6%	(11.4%, 15.8%)	10.4%	(9.0%, 11.8%)
Wrinkling	9.4%	(7.9%, 10.8%)	7.3%	(6.3%, 8.3%)	10.6%	(8.7%, 12.5%)	8.3%	(7.1%, 9.6%)
Implant Malposition	8.5%	(7.1%, 9.9%)	6.1%	(5.2%, 7.1%)	7.3%	(5.6%, 8.9%)	4.8%	(3.8%, 5.8%)
Breast Pain	7.9%	(6.5%, 9.3%)	5.5%	(4.6%, 6.4%)	7.8%	(6.1%, 9.4%)	5.6%	(4.5%, 6.6%)
Loss of Nipple Sensation/ Nipple Paresthesia/ Hypersensitivity	7.1%	(5.8%, 8.4%)	6.1%	(5.1%, 7.0%)	5.5%	(4.1%, 6.9%)	4.5%	(3.6%, 5.5%)
Hypertrophic Scarring	3.4%	(2.6%, 4.3%)	3.1%	(2.5%, 3.8%)	2.0%	(1.3%, 2.7%)	1.5%	(1.1%, 2.0%)
Capsule Calcification	3.2%	(2.3%, 4.2%)	2.3%	(1.7%, 2.9%)	3.4%	(2.3%, 4.5%)	2.4%	(1.7%, 3.1%)
Skin Paresthesia/ Hypersensitivity	3.0%	(2.2%, 3.7%)	2.6%	(2.0%, 3.2%)	2.0%	(1.2%, 2.8%)	1.3%	(0.8%, 1.8%)
Swelling	2.3%	(1.8%, 2.9%)	1.7%	(1.4%, 2.1%)	1.9%	(1.4%, 2.5%)	1.4%	(1.1%, 1.7%)
Other Complications	2.0%	(1.2%, 2.7%)	1.5%	(1.0%, 2.0%)	1.0%	(0.5%, 1.5%)	0.6%	(0.4%, 0.9%)
Implant Rupture	1.6%	(0.9%, 2.4%)	1.1%	(0.6%, 1.6%)	2.7%	(1.4%, 3.9%)	1.8%	(1.0%, 2.5%)
Implant Extrusion	1.3%	(0.6%, 2.0%)	0.9%	(0.5%, 1.3%)	0.6%	(0.3%, 1.0%)	0.6%	(0.3%, 0.8%)
Redness	1.2%	(0.8%, 1.7%)	0.8%	(0.5%, 1.1%)	1.0%	(0.6%, 1.5%)	0.6%	(0.4%, 0.9%)
Infection	1.0%	(0.6%, 1.4%)	0.7%	(0.4%, 0.9%)	0.7%	(0.3%, 1.2%)	0.4%	(0.2%, 0.7%)
Irritation	1.0%	(0.5%, 1.5%)	0.6%	(0.3%, 0.9%)	0.4%	(0.1%, 0.8%)	0.3%	(0.1%, 0.5%)
Pneumothorax	1.0%	(0.4%, 1.7%)	0.7%	(0.4%, 1.1%)	0.5%	(0.2%, 0.8%)	0.4%	(0.2%, 0.7%)
Delayed Wound Healing	0.8%	(0.4%, 1.2%)	0.6%	(0.4%, 0.9%)	0.6%	(0.2%, 1.1%)	0.4%	(0.1%, 0.6%)
Bruising	0.7%	(0.4%, 1.1%)	0.6%	(0.4%, 0.8%)	0.7%	(0.4%, 1.1%)	0.5%	(0.3%, 0.7%)
Seroma	0.7%	(0.4%, 1.0%)	0.4%	(0.2%, 0.6%)	0.5%	(0.1%, 0.9%)	0.3%	(0.1%, 0.5%)
Skin Rash	0.6%	(0.2%, 0.9%)	0.5%	(0.3%, 0.8%)	0.6%	(0.0%, 1.3%)	0.4%	(0.1%, 07%)
Hematoma	0.4%	(0.2%, 0.6%)	0.2%	(0.1%, 0.4%)	0.5%	(0.2%, 0.8%)	0.2%	(0.1%, 0.4%)
Lymphadenopathy	0.4%	(0.1%, 0.8%)	0.2%	(0.0%, 0.5%)	0.3%	(0.0%, 0.6%)	0.1%	(0.0%, 0.3%)
Tissue or Skin Necrosis	0.3%	(0.1%, 0.5%)	0.2%	(0.1%, 0.3%)	0.2%	(0.0%, 0.6%)	0.2%	(0.0%, 0.5%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

D. Safety Outcomes for Core Study

Safety outcomes assessed in the Core Study are reported for augmentation, reconstruction and revision in the tables provided below.

1. Cumulative Kaplan-Meier Risk of First Occurrence of Complications

The cumulative Kaplan-Meier risk of first occurrence of complications (and 95% confidence interval) is shown below.

Core Augmentation
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant

Complication	Augmentation			
	By Patient (N = 494)		By Implant (N = 987)	
	% (95% CI)		% (95% CI)	
Reoperation	20.6%	(16.8%, 24.4%)	16.6%	(14.1%, 19.0%)
Capsular Contracture	8.3%	(5.8%, 10.9%)	6.3%	(4.7%, 7.9%)
Implant Replacement/Removal	7.5%	(5.0%, 10.0%)	7.0%	(5.3%, 8.8%)
Swelling	6.8%	(4.5%, 9.0%)	5.6%	(4.2%, 7.1%)
Breast Pain	6.2%	(4.0%, 8.4%)	4.4%	(3.0%, 5.7%)
Loss of Nipple Sensation/ Nipple Paresthesia/Hypersensitivity	3.9%	(2.2%, 5.7%)	3.1%	(2.0%, 4.2%)
Implant Malposition	3.1%	(1.5%, 4.8%)	2.4%	(1.3%, 3.4%)
Asymmetry	2.8%	(1.3%, 4.4%)	N/A	
Hypertrophic/Abnormal Scarring	2.3%	(1.0%, 3.7%)	1.8%	(1.0%, 2.7%)
Ptosis	1.8%	(0.6%, 3.1%)	1.7%	(0.8%, 2.5%)
Skin Rash	1.7%	(0.5%, 2.8%)	1.6%	(0.8%, 2.3%)
Loss of Skin Sensation/ Skin Paresthesia/Hypersensitivity	1.7%	(0.5%, 2.8%)	1.4%	(0.6%, 2.1%)
Other Nipple Related Observation	1.3%	(0.3%, 2.3%)	1.0%	(0.3%, 1.6%)
Bruising	1.2%	(0.3%, 2.2%)	1.0%	(0.4%, 1.7%)
Implant Rupture	1.2%	(0.1%, 2.2%)	0.6%	(0.1%, 1.1%)
Redness	1.1%	(0.1%, 2.1%)	0.8%	(0.2%, 1.4%)
Delayed Wound Healing	1.1%	(0.1%, 2.1%)	0.7%	(0.1%, 1.2%)
Seroma/Fluid Accumulation	1.0%	(0.1%, 2.0%)	0.6%	(0.1%, 1.1%)
Hematoma	0.8%	(0.0%, 1.6%)	0.4%	(0.0%, 0.8%)
Wrinkling/Rippling	0.7%	(0.0%, 1.6%)	0.5%	(0.0%, 0.9%)
Implant Palpability/Visibility	0.6%	(0.0%, 1.3%)	0.4%	(0.0%, 0.8%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Core Augmentation
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant (continued)

Complication	Augmentation			
	By Patient (N = 494)		By Implant (N = 987)	
	%	(95% CI)	%	(95% CI)
Capsule Calcification	0.2%	(0.0%, 0.7%)	0.1%	(0.0%, 0.3%)
Lymphadenopathy	0.2%	(0.0%, 0.7%)	0.1%	(0.0%, 0.3%)
Infection	0.2%	(0.0%, 0.6%)	0.2%	(0.0%, 0.5%)
Implant Extrusion	0.2%	(0.0%, 0.6%)	0.1%	(0.0%, 0.3%)
Lymphedema	0.2%	(0.0%, 0.6%)	0.1%	(0.0%, 0.3%)
Tissue or Skin Necrosis	0.2%	(0.0%, 0.6%)	0.1%	(0.0%, 0.3%)
Irritation	0.0%	—	0.0%	—
Pneumothorax	0.0%	—	0.0%	—
Other Complications	0.0%	—	0.0%	—

Core Reconstruction
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant

Complication	Reconstruction			
	By Patient (N = 221)		By Implant (N = 361)	
	%	(95% CI)	%	(95% CI)
Reoperation	45.9%	(38.6%, 53.3%)	38.2%	(32.6%, 43.8%)
Implant Replacement/Removal	25.3%	(18.5%, 32.0%)	18.7%	(14.0%, 23.4%)
Capsular Contracture	16.1%	(10.7%, 21.6%)	11.2%	(7.6%, 14.8%)
Asymmetry	15.3%	(10.1%, 20.5%)	N/A	
Implant Rupture	6.3%	(2.8%, 9.8%)	4.2%	(2.0%, 6.5%)
Breast Pain	6.0%	(2.2%, 9.8%)	4.3%	(1.8%, 6.8%)
Implant Malposition	5.2%	(2.2%, 8.2%)	4.4%	(2.2%, 6.5%)
Other Nipple Related Observation	4.4%	(1.6%, 7.3%)	3.6%	(1.6%, 5.6%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Core Reconstruction
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant (continued)

Complication	Reconstruction			
	By Patient (N = 221)		By Implant (N = 361)	
	% (95% CI)		% (95% CI)	
Tissue or Skin Necrosis	4.3%	(1.5%, 7.0%)	2.9%	(1.1%, 4.7%)
Swelling	3.7%	(1.2%, 6.1%)	2.8%	(1.1%, 4.5%)
Wrinkling/Rippling	3.5%	(0.9%, 6.0%)	2.4%	(0.8%, 4.1%)
Hypertrophic/Abnormal Scarring	3.4%	(0.9%, 5.8%)	2.4%	(0.7%, 4.0%)
Infection	2.3%	(0.3%, 4.3%)	1.7%	(0.4%, 3.0%)
Delayed Wound Healing	2.3%	(0.3%, 4.3%)	1.4%	(0.2%, 2.7%)
Seroma/Fluid Accumulation	1.8%	(0.1%, 3.6%)	1.1%	(0.0%, 2.2%)
Bruising	1.4%	(0.0%, 2.9%)	1.1%	(0.0%, 2.2%)
Skin Rash	1.4%	(0.0%, 2.9%)	1.1%	(0.0%, 2.2%)
Other Abnormal Scarring	1.0%	(0.0%, 2.4%)	0.6%	(0.0%, 1.5%)
Ptosis	1.0%	(0.0%, 2.3%)	0.6%	(0.0%, 1.4%)
Redness	1.0%	(0.0%, 2.3%)	0.6%	(0.0%, 1.4%)
Pneumothorax	0.5%	(0.0%, 1.5%)	0.3%	(0.0%, 0.9%)
Implant Extrusion	0.5%	(0.0%, 1.4%)	0.3%	(0.0%, 0.8%)
Other Complications	0.5%	(0.0%, 1.4%)	0.3%	(0.0%, 0.9%)
Hematoma	0.5%	(0.0%, 1.3%)	0.3%	(0.0%, 0.8%)
Implant Palpability/Visibility	0.5%	(0.0%, 1.3%)	0.3%	(0.0%, 0.8%)
Capsule Calcification	0.0%	—	0.0%	—
Irritation	0.0%	—	0.0%	—
Loss of Nipple Sensation/ Nipple Paresthesia/Hypersensitivity	0.0%	—	0.0%	—
Loss of Skin Sensation/ Skin Paresthesia/Hypersensitivity	0.0%	—	0.0%	—
Lymphadenopathy	0.0%	—	0.0%	—
Lymphedema	0.0%	—	0.0%	—

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Core Revision
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant

Complication	Revision			
	By Patient (N = 225)		By Implant (N = 432)	
	%	(95% CI)	%	(95% CI)
Reoperation	33.4%	(26.9%, 39.8%)	26.7%	(22.4%, 31.1%)
Implant Replacement/Removal	13.4%	(8.7%, 18.1%)	11.9%	(8.6%, 15.1%)
Capsular Contracture	9.8%	(5.7%, 13.9%)	5.4%	(3.1%, 7.6%)
Breast Pain	7.2%	(3.7%, 10.8%)	5.0%	(2.8%, 7.1%)
Swelling	6.7%	(3.3%, 10.1%)	4.7%	(2.6%, 6.7%)
Seroma/Fluid Accumulation	5.3%	(2.2%, 8.3%)	3.0%	(1.3%, 4.7%)
Asymmetry	5.1%	(2.0%, 8.2%)	N/A	
Wrinkling/Rippling	5.0%	(2.0%, 8.0%)	3.8%	(1.8%, 5.7%)
Implant Malposition	4.9%	(1.9%, 7.8%)	3.3%	(1.5%, 5.1%)
Implant Rupture	3.6%	(1.0%, 6.3%)	2.2%	(0.7%, 3.7%)
Hypertrophic/Abnormal Scarring	3.2%	(0.7%, 5.7%)	2.3%	(0.7%, 3.9%)
Implant Palpability/Visibility	2.0%	(0.0%, 3.9%)	1.0%	(0.0%, 2.0%)
Tissue or Skin Necrosis	1.9%	(0.1%, 3.7%)	1.0%	(0.0%, 2.0%)
Infection	1.8%	(0.1%, 3.6%)	1.0%	(0.0%, 1.9%)
Bruising	1.4%	(0.0%, 2.9%)	0.9%	(0.0%, 1.8%)
Ptosis	1.0%	(0.0%, 2.3%)	0.7%	(0.0%, 1.6%)
Irritation	1.0%	(0.0%, 2.3%)	0.5%	(0.0%, 1.2%)
Delayed Wound Healing	0.9%	(0.0%, 2.2%)	0.5%	(0.0%, 1.1%)
Hematoma	0.9%	(0.0%, 2.1%)	0.5%	(0.0%, 1.1%)
Other Nipple Related Observation	0.5%	(0.0%, 1.4%)	0.5%	(0.0%, 1.2%)
Implant Extrusion	0.5%	(0.0%, 1.4%)	0.3%	(0.0%, 0.7%)
Skin Rash	0.5%	(0.0%, 1.4%)	0.2%	(0.0%, 0.7%)
Loss of Skin Sensation/ Skin Paresthesia/Hypersensitivity	0.5%	(0.0%, 1.3%)	0.2%	(0.0%, 0.7%)
Other Complications	0.4%	(0.0%, 1.3%)	0.2%	(0.0%, 0.7%)
Capsule Calcification	0.0%	—	0.0%	—
Loss of Nipple Sensation/ Nipple Paresthesia/Hypersensitivity	0.0%	—	0.0%	—
Lymphadenopathy	0.0%	—	0.0%	—
Lymphedema	0.0%	—	0.0%	—

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Core Revision
3-Year Cumulative First Occurrence Kaplan-Meier Complication Risk Rates (95% Confidence Interval), By Patient and By Implant (continued)

Complication	Revision	
	By Patient (N = 225)	By Implant (N = 432)
	% (95% CI)	% (95% CI)
Pneumothorax	0.0% —	0.0% —
Redness	0.0% —	0.0% —

2. **Types of Reoperations Through 3 Years**
Of the 494 augmentation patients in the Core Study, there were 94 patients (19.0%) who had 112 reoperations during the first 3 years of follow-up. Of the 221 reconstruction patients, there were 92 patients (41.6%) who had 127 reoperations through 3 years, excluding planned procedures such as nipple reconstruction and nipple tattoo. Of the 225 revision patients, there were 70 patients (31.1%) who had 100 reoperations through 3 years. The table below shows the types of reoperations performed through 3 years post-implant in the Core Study based on the total number of reoperations.

Types of Reoperations Through 3 Years

Type of Reoperation[1]	Augmentation N = 112 reoperations		Reconstruction N = 127 reoperations		Revision N = 100 reoperations	
	n	%	n	%	n	%
Implant Replacement/ Removal	32	28.6%	46	36.2%	29	29.0%
Capsule Procedure[2]	26	23.2%	16	12.6%	20	20.0%
Mastopexy	15	13.4%	1	0.8%	8	8.0%
Scar Revision	11	9.8%	26	20.5%	10	10.0%
Biopsy	10	8.9%	0	0%	2	2.0%

[1] Primary procedure performed
[2] Capsule Procedure includes capsulectomy, capsulotomy, and capsulorraphy

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Types of Reoperations Through 3 Years (continued)

Type of Reoperation[3]	Augmentation N = 112 reoperations		Reconstruction N = 127 reoperations		Revision N = 100 reoperations	
	n	%	n	%	n	%
Aspiration of Hematoma/Seroma	5	4.5%	6	4.7%	8	8.0%
Reposition Implant	5	4.5%	6	4.7%	3	3.0%
Pocket Revision	3	2.7%	2	1.6%	6	6.0%
Wound Repair	2	1.8%	7	5.5%	3	3.0%
Revision of Nipple Reconstruction/Tattoo	1	0.9%	6	4.7%	7	7.0%
Other	1	0.9%	2	1.6%	1	1.0%
Surgical Exploration of Breast Area or Implant	1	0.9%	1	0.8%	0	0%
Removal of Excess Tissue/Lesion/Cyst	0	0%	4	3.1%	2	2.0%
Liposuction	0	0%	3	2.4%	0	0%
Breast Reduction	0	0%	1	0.8%	1	1.0%
Total	**112**	**100%**	**127**	**100%**	**100**	**100%**

3. **Reasons for Implant Replacement/Removal Through 3 Years**
Of the 494 augmentation patients in the Core Study, there were 32 patients (6.5%) who had 60 implants removed over 3 years; of these, 51 implants (85.0%) were replaced. Of the 221 reconstruction patients, there were 46 patients (20.8%) who had 56 implants removed through 3 years; 51 implants (91.1%) were replaced. Of the 225 revision patients, there were 27 patients (12.0%) who had 46 implants removed through 3 years; 41 implants (89.1%) were replaced. The primary reason for implant replacement/removal is shown in the following table, based on the total number of implants removed.

[3] Primary procedure performed

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Reasons for Implant Replacement/Removal Through 3 Years

Primary Reason for Implant Replacement/Removal	Augmentation N = 60 removals		Reconstruction N = 56 removals		Revision N = 46 removals	
	n	%	n	%	n	%
Capsular Contracture	27	45.0%	12	21.4%	7	15.2%
Style/Size Change (Patient Request)	13	21.7%	4	7.1%	13	28.3%
Malposition	6	10.0%	8	14.3%	8	17.4%
Media Anxiety (Patient Request)	5	8.3%	0	0%	0	0%
Asymmetry	3	5.0%	13	23.2%	1	2.2%
Implant Rupture	2	3.3%	5	8.9%	6	13.0%
Ptosis	2	3.3%	0	0%	6	13.0%
Breast Cancer	1	1.7%	2	3.6%	0	0%
Extrusion	1	1.7%	1	1.8%	0	0%
Wrinkling	0	0%	3	5.4%	0	0%
Pain	0	0%	2	3.6%	1	2.2%
Breast Tissue Contour Deformity	0	0%	2	3.6%	0	0%
Hematoma/Seroma	0	0%	2	3.6%	0	0%
Unsatisfactory Scar	0	0%	1	1.8%	2	4.4%
Injury (Iatrogenic or Traumatic)	0	0%	1	1.8%	0	0%
Delayed Wound Healing	0	0%	0	0%	1	2.2%
Infection	0	0%	0	0%	1	2.2%
Total	**60**	**100%**	**56**	**100%**	**46**	**100%**

5. **CTD and Breast Disease**
   The two tables provided below summarize post-implant observations from the Core Study 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. CTD reports were based on a diagnosis by a physician. There were no unconfirmed CTD self-reports by the patients.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

Reports of CTD Through 3 Years, By Patient

Rheumatic Disease Reports	Augmentation	Reconstruction	Revision
	n	n	n
Rheumatoid Arthritis	1	0	0
Systemic Sclerosis/Scleroderma	0	1	0
Fibromyalgia	0	0	1

Reports of Breast Disease Through 3 Years, By Patient

Breast Disease Reports	Augmentation		Reconstruction		Revision	
	n	%	n	%	n	%
Benign	29	5.9%	10	4.5%	16	7.1%
Malignant	1	0.2%	5	2.3%	0	0%
Unknown Outcome	2	0.4%	2	0.9%	0	0%

E. Effectiveness Outcomes for Adjunct Study

Effectiveness in the Adjunct Study was assessed by patient reports of satisfaction at 1 and 3 years post-implant. Data is only included for those patients who have reached the scheduled follow-up visit interval and for whom satisfaction data was obtained at a follow-up visit.

A total of 5,501 of the original 15,465 reconstruction patients were included in an analysis of satisfaction at 1 year post-implant, with 92.8% of these patients indicating that they were satisfied with their breast implant surgery. Of the 732 reconstruction patients included in the satisfaction analysis at 3 years post-implant, 92.8% indicated that they were satisfied with their breast implant surgery.

A total of 3,150 of the original 9,881 revision patients were included in an analysis of satisfaction at 1 year post-implant, with 90.1% of these patients indicating that they were satisfied with their breast implant surgery. Of the 498 revision patients included in the satisfaction analysis at 3 years post-implant, 88.2% indicated that they were satisfied with their breast implant surgery.

F. Effectiveness Outcomes for Core Study

Effectiveness in the Core Study was assessed by breast size change (augmentation patients only), patient satisfaction, and patient body image, body esteem, and self concept. These outcomes were assessed before implantation and at 1 and 2 years after surgery, except for breast size, which was measured within the first year and a half after surgery.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

For augmentation patients, 408 of the 494 patients (82.6%) had a breast measurement within 18 months after surgery. Of these 408 patients, 165 (40.4%) increased their breast measurement by one bra cup size, 185 (45.3%) increased by two bra cup sizes, and 34 (8.3%) increased by more than two bra cup sizes. The remaining 24 patients (5.9%) did not increase their bra cup size post-implant.

For augmentation patients, 425 of the 494 patients (86.0%) provided a satisfaction rating at 2 years post-implant, with 96.0% of these patients indicating that they were satisfied with their breast implant surgery.

At baseline, augmentation patients scored significantly higher than did the general U.S. female population on the SF-36, which measures general health-related quality of life and well being. After implantation, patients had a worsening of some SF-36 scores; however, the magnitude of the differences was small and the post-implant quality of life scores remained well above those of the general U.S. female population. There was also a slight decrease post-implant on some of the subscales for the MOS-20, another survey of general health-related quality of life and well being. Results for the Tennessee Self-Concept Scale revealed a statistically significant increase pre- vs. post-implant in patients' physical self-concept. There was no significant change pre- *vs.* post-implant in patient's self-esteem as measured by the Rosenberg Self-Esteem Scale, or in their evaluation of themselves relative to their breasts. On the Body Esteem Scale, findings indicated a significant improvement in patients' overall body esteem post-implant, with the largest increase in the sexual attractiveness subscale. In terms of patients' expectation and perceived results of breast implant surgery, significant positive change was observed pre- vs. post-implant in subscales that measured self image, social relations, and daily living. On the quality of life measurement of patient satisfaction, there were significant positive increases post-implant in patient satisfaction with her breasts, breast size, breast shape, breast feel, and how well her breasts matched.

For reconstruction patients, 177 of the 221 patients (80.1%) provided a satisfaction rating at 2 years post-implant, with 94.3% indicating that they were satisfied with their breast implant surgery.

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 (559) were single lumen silicone gel filled implants (40.7%), closely followed by 505 saline/silicone-gel multilumen (double, triple, or quadruple lumens) implants (36.7%). Sixteen percent were saline breast implants.

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

Of the 559 single lumen gel-filled implants, 162 (29%) were removed by 10 years, which includes implants removed as part of planned reconstruction. After 10 years 397 single lumen gel devices (71%) were still implanted. Of the 143 (25.6%) gel implants removed for reasons other than planned reconstruction, the most common reason for removal was capsular contracture (51 implants; 31.4%). This was followed by aesthetic (32 implants; 19.7%), healing (22 implants; 13.6%), mechanical and other (19 implants, 11.8%), media raised concerns (8 implants; 4.9%), unknown/other (8 implants; 4.9%), and finally malignancy (3 implants; 1.9%).

Removal for aesthetic reasons included implant migration/repositioning, dimpling, asymmetry, and contour/size problems. Healing related included infection, improper healing, necrosis, bleeding and rejection of the implant. Mechanical reasons included rupture, leakage, deflation, and injury (accident or puncture). Media raised concerns included autoimmune disease or symptoms, concern or fear/ media reports and allergic reaction. Removal for unknown/other reasons included personal preference, non-implant related infection, muscle structure, and chest wall or mastectomy defect/deformity. Malignancy included recurrent disease.

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 has 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

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

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 for a woman with an implanted breast to breast feed an infant? 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. 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.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
(continued)

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. Regardless of whether an implant is still in place or whether it has been removed, another issue of concern during mammography is the presence of calcification of the implant capsule. If the capsule is left in place, it might lead to false positive diagnoses of malignancy or false negatives.

C. **MDR [Pending from FDA]**

XIII. PANEL RECOMMENDATION [Pending from FDA]

XIV. CDRH DECISION [Pending from FDA]

XV. APPROVAL SPECIFICATIONS [Pending from FDA]