SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Silicone Gel-Filled Breast Implants
Device Trade Name:	Inamed® Silicone-Filled Breast Implants
Applicant's Name and Address:	Allergan* 5540 Ekwill Street Santa Barbara, California 93111
Premarket Approval Application (PMA) Number:	P020056
Dates of Panel Recommendation:	October 15, 2003 and April 12, 2005
Date of Notice of Approval to Applicant:	November 17, 2006

II. INDICATIONS FOR USE

The Inamed® Silicone-Filled Breast Implants are indicated for females for the following uses (procedures):

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

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

III. CONTRAINDICATIONS

Breast implant surgery should not be performed in:

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Inamed® Silicone-Filled Breast Implants physician labeling.

* formerly Inamed Corporation

V. DEVICE DESCRIPTION

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

Table 1: Approved Inamed® Silicone-Filled Breast Implants

Style	Description	Size Range
10	Smooth, Round, Moderate Projection	120-800cc
15	Smooth, Round, Midrange Projection	158-752cc
20	Smooth, Round, Full Projection	120-800cc
40	Smooth, Round, Moderate Projection	80-560cc
45	Smooth, Round, Full Projection	120-800cc
110	Textured, Round, Moderate Projection	90-510cc
115	Textured, Round, Midrange Project	150-716cc
120	Textured, Round, High Projection	180-650cc

Table 2: Device Materials

Component	Material
Shell, inner/outer layers	Dimethyl Silicone Elastomer Dispersion
Shell, barrier layer	Diphenyl Silicone Elastomer Dispersion
Shell textured layer	MED-6400 Silicone Elastomer
Patch assembly	MED 2174 and MED 2-6650 Silicone Elastomer
Gel	Silicone Gel: Base and Crosslinker; platinum cure

VI. ALTERNATIVE PRACTICES OR PROCEDURES

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

VII. REGULATORY AND MARKETING HISTORY

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

The Allergan Adjunct Study, which was started in 1998, was designed to address the public health need of reconstruction and revision patients. Local complications and satisfaction data were collected at 1, 3, and 5-year timepoints. However, with the approval of the

subject PMA P020056, the public health need no longer exists and, while patient follow-up continues through 5 years for those Adjunct Study patients currently enrolled, no new patients will be enrolled into the Allergan Adjunct Study.

In June 1998, Allergan received FDA approval and began their Core Study for their silicone gel-filled breast implant product. The Core Study is the primary clinical data set in this PMA.

Outside of the U.S., over 379,000 Inamed® Silicone-Filled Breast Implants have been distributed worldwide from 1998 through 2005. The Allergan product has not been withdrawn from any foreign market for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

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

IX. SUMMARY OF PRECLINICAL STUDIES

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

A. Chemistry Data

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

1. Extent of Crosslinking

Shell and Patch - The physical strength (tensile strength) and elasticity (elongation at failure) of the shell and patch materials are 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 are measured to ensure they meet or exceed pre-

established material specifications prior to being released for use in the manufacture of the implant shells. 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 3.0 lb break force and 380% elongation.

Gel - Every lot of gel received by Allergan 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 uniformity of the crosslink density across all lots of gel used in the implants is ensured by this testing performed on each breast implant lot produced. All lots of gel used in the implants have an extent of crosslinking sufficient to achieve the internal specification.

2. Volatiles

Analysis for volatiles present in the shell and patch material showed that the shell contained up to 279µg of 1,1,1 trichloroethane and 251µg of isopropyl alcohol. Analysis for volatiles present in gel was not necessary because the gel materials do not contain any organic solvents.

3. Extractables

Finished sterilized devices were analyzed for extractables. The shell and the gel components of the device were separated and subjected to chemical analysis. 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. A polar solvent (ethanol) and a non-polar solvent (hexane) were used for exhaustive extraction. The highest level of extractable residue was obtained using hexane as the extracting solvent. Everything detected in the polar solvent residue was also detected in the non-polar solvent residue. The hexane residue was subjected to the analyses below.

Gravimetric Analysis - The amounts of hexane extractables (after exhaustive extraction) from virgin shell/patch and implant shell/patch were 3.53%-3.75% and 8.85%-9.20%, respectively. The amounts of hexane extractables (after exhaustive extraction) from the gel were 71.25%-85.32%.

Fourier Transform Infra-Red (FTIR) Analysis - The hexane extractables from the virgin shell-patch and implant shell-patch on FTIR analysis showed characteristic peaks of polydimethylsiloxanes (PDMS). The bands for phenyl groups at 3072 cm^{-1} and 3052 cm^{-1} were not present in the spectra because of very low concentrations of oligophenylsiloxanes.

Gel Permeation Chromatography - The hexane extracts of implant shell and patch samples showed a bimodal molecular weight distribution; the polydispersities were 1.35 for the high molecular weight peak and 1.27 for the low molecular weight peak. The hexane extracts of virgin shell and patch samples also showed a bimodal molecular weight distribution; the polydispersities were 1.56 for the high molecular weight peak and 1.45 for the low molecular weight peak. The hexane residue of the gel on GPC analysis gave multiple incompletely resolved peaks, indicating very high polydispersity.

Qualitative and Quantitative Analyses of Extractables - The hexane residue was subjected to GC-MS (gas chromatography-mass spectrometry) analysis. Table 3 below lists the qualitative and quantitative data. Cyclic PDMS from D_9 – D_{21} were present in the gel-exposed shell, virgin shell, and gel residues. Linear dimethylsiloxanes L_9 - L_{18} were present in the gel and the gel-exposed shell, but not in virgin shell. Also seen were diphenylsiloxanes present in the gel residue. This analysis and the gravimetric analysis indicated that there was interaction between the shell and the gel components of the device. The concentration of the smaller molecular weight oligomers was highly comparable to the concentration of oligomers present in the FDA-approved saline-filled breast implants.

Table 3: Concentrations of Low Molecular Weight Components Detected (in ppm by component weight).

Identification	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
D3	ND (<146)	ND (<17)	ND (<7)
D4	ND (<69)	ND (<8)	ND (<3)
D5	ND (<6)	ND (<1)	ND (<1)
D6	ND (<6)	ND (<1)	ND (<1)
D7	ND (<6)	ND (<1)	ND (<1)
D8	ND (<8)	ND (<1)	ND (<1)
D9	ND (<8)	6	ND (<1)
D10	ND (<8)	12	2
D11	11	21	9
D12	32	94	26
D13	64	62	65
D14	237	186	209
D15	366	278	285
D16	491	351	317
D17	593	432	328
D18	729	527	342
D19	678	601	0
D20	735	605	212
D21	668	474	129
L1	ND (<63)	ND (<7)	ND (<3)
L2	ND (<8)	ND (<1)	ND (<1)
L3	ND (<8)	ND (<1)	ND (<1)
L4	ND (<10)	ND (<1)	ND (<1)
L5	ND (<8)	ND (<1)	ND (<1)
L6	ND (<7)	ND (<1)	ND (<1)
L7	ND (<8)	2	4
L8	ND (<8)	2	ND (<1)
L9	ND (<9)	8	ND (<1)
L10	19	17	ND (<1)
L11	35	29	ND (<1)
L12	63	49	ND (<1)
L13	103	84	ND (<1)
L14	132	108	ND (<1)
L15	169	128	ND (<1)
L16	183	106	ND (<1)
L17	161	137	ND (<1)

Identification	Gel (ppm)	Implant Shell & Patch (ppm)	Virgin Shell & Patch (ppm)
L18	177	128	ND (<1)
Diphenyl siloxanes	242	985	2762

ND (<X) = Not detected at less than X, the concentration in parts per million.

4. Heavy Metal Analysis

Complete metal analyses were provided on the individual components of the device. The metal concentrations obtained from the atomic absorption of digested device materials are shown in Table 4 below.

Table 4. Heavy Metal Concentrations

Metal	Virgin Shell (standard dispersion) (ppm)	Virgin Shell (barrier dispersion) (ppm)	Patch (ppm)	Gel (ppm)
Antimony	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Arsenic	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Barium	1	1	2	1
Beryllium	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Cadmium	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Calcium	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Chromium	0.3	0.4	1.8	0.2
Cobalt	ND (<0.2)	ND (<0.2)	ND (<0.2)	ND (<0.2)
Copper	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Iron	ND (<0.1)	0.2	8.7	1.2
Lead	ND (<0.2)	ND (<0.2)	ND (<0.2)	0.3
Magnesium	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Manganese	ND (<0.05)	ND (<0.05)	0.15	ND (<0.05)
Mercury	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Molybdenum	ND (<0.5)	ND (<0.5)	ND (<0.5)	ND (<0.5)
Nickel	ND (<0.2)	1	0.7	ND (<0.2)
Potassium	ND (<1)	8	1	ND (<1)
Selenium	ND (<0.1)	ND (<0.1)	ND (<0.1)	ND (<0.1)
Silver	ND (<0.1)	0.2	ND (<0.1)	ND (<0.1)
Sodium	ND (<10)	ND (<10)	ND (<10)	ND (<10)
Thallium	ND (<1)	ND (<1)	ND (<1)	ND (<1)
Vanadium	ND (<0.4)	ND (<0.4)	ND (<0.4)	ND (<0.4)
Zinc	0.12	ND (<0.05)	3.9	0.22

ND (<X) = Not detected at less than X, the concentration in parts per million.

In addition, catalyst metal analyses were carried out using ICP-MS on digested finished device materials of the unextracted shell and the gel components of the device. The shell and patch were found to contain 5.9 ppm of platinum, the patch was found to contain 6.6 ppm of tin, and the gel was found to contain 4.0 ppm of platinum.

As a note, platinum is a metal used as a catalyst in the manufacture of the shell and gel components of silicone breast implants. The small amounts of platinum remaining in the product following manufacturing may enter the body, either by diffusing through the intact shell (i.e., through gel bleed) or through an implant rupture. Based on our review of the gel

bleed testing, the published literature on this topic, as well as the biocompatibility testing and clinical data on the device, FDA concluded that the platinum contained in breast implants is in the zero oxidation state, which has the lowest toxicity and, thus, does not pose a significant risk to women with silicone breast implants.

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

5. Silica Filler

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

B. Toxicology Data

Allergan provided both pharmacokinetic and biocompatibility testing to address the biological safety of the device materials.

Pharmacokinetics

A pharmacokinetic study was designed to follow the absorption and distribution of ^{14}C-labeled silicone gel implanted subcutaneously along the lumbar spine of 5 rats. The average dose was 3.4g of gel per 125g rat, which was equivalent to 27g/kg. Two of the rats were debilitated, so the results are based on only 3 animals. The ^{14}C-labeled silicone compound (trimethylsiloxy endblocked polydimethylsiloxane) was formulated to be identical to the standard polymer silicone used to manufacture the implant gel. Following the subcutaneous implanting of the ^{14}C-labeled gel, absorption, distribution, and excretion of the silicone gel were studied for up to 30 days. After 30 days, virtually all the labeled material was still at the implantation site. The amount of radioactivity collected from all other sites in the body accounted only for 0.06% of the administered dose. Levels of radioactivity peaked in the blood at day 21 and then declined. It is important to note that this gel was not encased in a shell, but was placed into the animal as a gel, yet only insignificant amounts of radioactivity were detected elsewhere in the organs at the end of 30 days.

Biocompatibility Testing

The biocompatibility testing below was conducted for the major device components (shell, gel and patch), as described in ISO 10993.[1] This testing demonstrated the biocompatibility of the materials in the Allergan product.

1. Cytotoxicity

Minimum essential medium (MEM) extracts were evaluated for cytotoxic effects on mouse fibroblast cells (L929). The results showed that the test articles (gel and shell components) were non-cytotoxic.

2. Irritation

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

3. Acute Systemic Toxicity

Saline, sesame seed oil, PEG, and alcohol in saline (1:10) extracts of test articles (gel and shell components) were evaluated for systemic toxicity in mice. There was no animal mortality or other toxic responses. The results showed that the test articles were not toxic.

4. Hemocompatibility

Whole rabbit blood in saline was exposed for 1 hour at 37°C to test articles (gel and shell components). The blood and saline mixture was examined spectroscopically for cell lysis. The results showed that the test articles were non-hemolytic.

5. Pyrogenicity

Saline eluates of test articles (gel and shell components) were injected intravenously via the marginal ear vein of rabbits. The temperature of the animals was monitored. The eluate did not produce a febrile response. The results showed that the test articles were non-pyrogenic.

6. Immunotoxicity

Test articles (gel and shell components) were evaluated for 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, B-cell enumeration, and the 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.

7. Sensitization

Saline and sesame seed oil extracts of the test articles (gel and shell components) 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. Muscle Implantation

Test articles (gel and shell components) 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 Toxicity and Chronic Toxicity and Carcinogenicity sections. The findings of all studies were that the test articles did not elicit a toxic response.

9. Subchronic Toxicity

Test articles (gel and shell components) were subcutaneously implanted and evaluated for subchronic toxicity. In addition, 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.

The elastomeric test articles 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 surrounded, but did not penetrate, the gel. The physiologic response to the pulverized low-density polyethylene control consisted of some connective tissue that penetrated between separate pulverized particles.

10. Reproductive Toxicology and Teratogenicity

An extended F_1-generation evaluation was performed with patched shells obtained from final devices. In that evaluation, F_1-generation rats were exposed to the pulverized test article in-utero. Female F_1-generation animals were also implanted with the test article, and 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. 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.

With respect to teratogenicity, silicone gel was subcutaneously implanted in female Sprague-Dawley rats. The animals were exposed to a 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, a developmental study was performed with patched shells obtained from gel-filled final devices and a teratology study was performed with saline-filled final devices. The test articles were pulverized and subcutaneously implanted 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 toxicological effects.

11. Genotoxicity

Allergan addressed genotoxicity testing using the Salmonella Reverse Mutation Assay (Ames Test), CHO/HGPRT Forward Mutation Assay, and Chromosome Abberration Frequencies in CHO cells.

In the first set of data, Allergan provided results on bacterial mutagenesis studies with DMSO extracts of gel and shell components. Additionally, a study was performed with a combined ethanol extract of gel and shell components. None of the extracts, with or without microsomal fraction activation, were mutagenic to any of the bacterial tester strains. FDA determined that bacterial mutagenesis has been adequately addressed.

In a second set of data, Allergan provided results on the CHO/HGPRT Forward Mutation Assay with a combined ethanol extract of gel and shell components. None of the extracts, with or without microsomal activation, were mutagenic or cytotoxic to the CHO cell cultures. FDA determined that mammalian mutagenesis has been adequately addressed.

In a third set of data, Allergan provided results on an in-vitro cytogenetic assay that measured chromosomal aberration frequencies in CHO cells with a combined ethanol extract of gel and shell components. No significant increase in cells with chromosomal aberrations was seen at any dose level in either the absence or presence of rat liver microsomes. FDA determined that DNA damage has been adequately addressed by this assay.

12. Chronic Toxicity and Carcinogenicity

Test articles (gel and shell components) 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. As previously stated, solid state tumorigenicity 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.

C. Mechanical Data

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

1. Fatigue Rupture

Styles 40 (80cc) and 110 (90cc) were chosen for fatigue testing as representative of Allergan's product line. All implants tested were final, sterilized versions with the minimum allowable radial shell thickness. The test set-up consisted of a uniaxial test fixture of parallel plates. Testing was performed under ambient laboratory conditions in air. The applied cyclic loads ranged from 20-55 lbs. Testing was performed at 1 Hz for all applied loads. A minimum of 3 implants for each style was tested for each load level. Runout was defined as 6.5 million cycles. The resulting endurance load levels were 55 lbs for smooth implants and 30 lbs for textured implants. As expected, based on the test set-up, all fatigue failure modes were radial tears. FDA believes that these data demonstrated that the Allergan product can withstand large static loading and in-vivo cyclic loading. See Section XI below for more details.

2. Gel Bleed Testing

Allergan provided testing to identity the gel bleed constituents (including the platinum species [or other catalysts]), the rate that the gel constituents bleed out, and how that rate changes over time. Allergan's test method, which was designed to mimic in-vivo exposure to silicone gel-filled breast implants, involved the incubation of smooth implants in bovine serum at 37°C. At specific timepoints, samples of the solution were withdrawn for analysis for low molecular weight (LMW) silicones and platinum. The results indicated that the diffusion of measured constituents essentially ceased by 90 days and that measurable amounts of silicones from D4 to D21 and from MD2M to MD19M diffused into the serum over that period. The maximum cumulative amount of LMW silicones was 48.1µg after 90 days. The maximum cumulative amount of platinum was 1.1µg after 90 days. Over 99% of the LMW silicones and platinum stayed in the implant.

With regard to the health consequences of gel bleed, the literature has reported small quantities of LMW silicone compounds, as well as platinum (in zero oxidation state), have been found to diffuse ("bleed") through an intact implant shell.[2,3] The evidence is mixed as to whether there are any clinical consequences associated with gel bleed. For instance, studies on implants implanted for a long duration have suggested that such bleed may be a contributing factor in the development of capsular contracture and lymphadenopathy.[4] However, evidence against gel bleed being a significant contributing factor to capsular contracture and other local complications is provided by the fact that there are similar or lower complication rates for silicone gel-filled breast implants than for saline-filled breast implants. Saline-filled breast implants do not contain silicone gel and, therefore, gel bleed is not an issue for those products. Furthermore, toxicology testing has indicated that the silicone material used in the Allergan implants does not cause toxic reactions in test animals. It should also be noted that studies reported in the literature have demonstrated that the low concentration of platinum contained in breast implants is in the zero oxidation (most biocompatible) state.[5,6,7,8] The overall body of available evidence supports that the extremely low level of gel bleed for Allergan's product is of no clinical consequence.

3. Gel Cohesivity

Gel cohesivity and penetration testing assess the cohesive and cure characteristics of silicone gel, respectively. Gel cohesivity testing was performed as per ASTM F703 (cone/pendant method) using gel from final finished product. Of the 112 samples tested, the average pendant length was 0.34cm (range of 0.0-1.1cm), which meets the ASTM F703 specification of <4.5cm. Gel penetration testing was performed as per an Allergan test method involving measurement of the penetration of a plunger into in-process gel in a jar. All samples passed Allergan's internal penetration specification.

D. Modes and Causes of Rupture

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

The primary set of modes and causes of rupture data was a retrieval study that involved 92 explanted, single-lumen Adjunct and Core Study devices that were determined to have failed upon laboratory observation (intact devices were excluded from this dataset). The samples analyzed were explanted anywhere from time 0 (damaged during the implantation procedure and, thus, not implanted) up to 10 years after implantation. For these 92 explants, the failure modes were surgical instrument damage (n=53); fold flaw (n=4); manufacturing (n=7); surgical impact (n=5); and sharp edge openings (n=23). FDA determined that these data are adequate to characterize the modes and causes of rupture through approximately 10 years. See Section XI below for more details.

E. Shelf Life Data

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

X. SUMMARY OF THE ALLERGAN CORE STUDY

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

A. Study Design

The Allergan Core Study is a 10-year study to assess safety and effectiveness in 940 augmentation, reconstruction, and revision (revision-augmentation and revision-reconstruction) patients. The Core Study originally included a double-lumen, contour-shaped style implant (Style 153) as one of the proposed product styles. However, Allergan withdrew Style 153 from its PMA application. Therefore, the clinical study data presented

include only the round styles. Accordingly, the Allergan Core Study now consists of 715 patients. Patient medical histories and baseline clinical data were collected preoperatively. Patient follow-up is at 6 months, 1 year, 2 years, and annually through 10 years. Rupture is assessed for patients who have scheduled MRIs at years 1, 3, 5, 7, and 9 years to screen for silent rupture (i.e., MRI cohort) and those who are not assessed for rupture by scheduled MRIs (i.e., non-MRI cohort).

Safety assessments include complication rates, reasons for reoperation, and reasons for implant removal. Effectiveness assessments include circumferential chest size change and bra cup size change (augmentation patients only), patient satisfaction, and quality of life (QoL). QoL is comprised of measures of self-esteem, body image, and general health outcome. The results through 4 years are currently being reported, and the study remains ongoing. Allergan will periodically update labeling as more information becomes available.

B. Patient Accounting and Baseline Demographic Profile

The Allergan Core Study consists of 715 patients, including 455 primary augmentation patients, 147 revision-augmentation patients, 98 primary reconstruction patients, and 15 revision-reconstruction patients. Four-year data are available for 83% of the eligible primary augmentation patients, 82% of the eligible revision-augmentation patients, 89% of the eligible primary reconstruction patients, and 100% of the revision-reconstruction patients.

Demographic information for the Core Study with regard to race is as follows: 86% of the Core Study patients were Caucasian; 5% were Hispanic; 3% were Asian; <1% were African American; and 5% were other. The mean age at surgery was 34 years for primary augmentation patients, 42 for revision-augmentation patients, 50 years for primary reconstruction patients, and 56 years for revision-reconstruction patients. Approximately 56% of the Core Study patients were married. Approximately 83% had some college education.

With respect to surgical baseline factors, for primary augmentation patients, the most frequently used devices were smooth implants (59%), the most common incision site was inframammary (46%), and the most frequent site of placement was submuscular (70%). For revision-augmentation patients, the most frequently used devices were smooth implants (57%), the most common incision site was inframammary (64%), and the most frequent site of placement was submuscular (60%). For primary reconstruction patients, the most frequently used devices were textured implants (64%), the most common incision site was the mastectomy scar (59%), and the most frequent site of placement was submuscular (83%). For revision-reconstruction patients, the most frequently used devices were textured implants (56%), the most common incision site was mastectomy scar (52%), and the most frequent site of placement was submuscular (76%).

C. Complication Rates

Table 5 below shows the 4-year, by-patient, cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of complications for primary augmentation, revision-augmentation, and primary reconstruction. For revision-reconstruction, cumulative incidence rates are presented.

Table 5: KM Risk Rates through 4 Years

KM Rates through 4 Years[1]		Primary Augmentation[2]	Revision-Augmentation[3]	Primary Reconstruction[4]	Revision-Reconstruction[5]
		N=455	N=147	N=98	N=15 (incidence rates)
Any complication (including reoperation)		41.3% (36.7, 45.9)	56.9% (48.6, 65.1)	58.3% (48.3, 68.2)	60.0% (32.3, 83.7)
Any reoperation		23.5% (19.5, 27.5)	35.3% (27.3, 43.3)	40.9% (31.0, 50.8)	33.3% (11.8, 61.6)
Implant removal with or without replacement		9.6% (6.8, 12.4)	13.3% (7.6, 19.0%)	24.8% (15.9, 33.6)	0
Asymmetry		3.2% (1.6, 4.9)	5.1% (1.4, 8.8)	16.4% (8.7, 24.0)	13.3% (1.7, 40.5)
Breast pain		8.2% (5.6, 10.7)	7.8% (3.3, 12.2)	3.1% (0.0, 6.5)	6.7% (0.2, 31.9)
Bruising		0.7% (0.0, 1.4)	2.1% (0.0, 4.4)	1.0% (0.0, 3.0)	6.7% (0.2, 31.9)
Capsular contracture III/IV		13.2% (10.0, 16.3)	17.0% (10.7, 23.4)	14.1% (7.0, 21.2)	6.7% (0.2, 31.9)
Delayed wound healing		0.9% (0.0, 1.8)	0.7% (0.0, 2.0)	0	6.7% (0.2, 31.9)
Hematoma		1.6% (0.4, 2.7)	2.1% (0.0, 4.4)	0	0
Scarring/hypertrophic scarring		3.7% (1.9, 5.5)	6.1% (2.0, 10.1)	2.1% (0.0, 4.9)	6.7% (0.2, 31.9)
Implant extrusion		0.2% (0.0, 0.7)	0	2.3% (0.0, 5.4)	0
Implant malposition		4.1% (2.3, 6.0)	4.6% (1.0, 8.2)	3.3% (0.0, 7.0)	13.3% (1.7, 40.5)
Implant palpability/visibility		0.7% (0.0, 1.4)	6.0% (2.0, 10.1)	0	6.7% (0.2, 31.9)
Implant rupture	MRI cohort	2.7% (0.1, 5.3)	4.0% (0.0, 9.5)	0	0
	Non-MRI cohort	0.4% (0.0, 1.1)	1.2% (0.0, 3.6)	0	10.0% (0.3, 44.5)
Infection		0.5% (0.0, 1.2)	1.4% (0.0, 3.3)	4.2% (0.2, 8.3)	0
Irritation		0	0.7% (0.0, 2.1)	0	0
Nipple complications		4.9% (2.9, 6.9)	0	1.0% (0.0, 3.0)	0
Breast/skin sensation changes		1.4% (0.3, 2.4)	1.4% (0.0, 3.3)	0	0
Necrosis		0.5% (0.0, 1.1)	0	2.3% (0.0, 5.4)	0
Ptosis		1.4% (0.3, 2.5)	3.1% (0.1, 6.2)	1.0% (0.0, 3.0)	0
Redness		0.9% (0.0, 1.8)	0.8% (0.0, 2.3)	1.1% (0.0, 3.3)	0
Seroma		1.3% (0.3, 2.4)	5.0% (1.4, 8.6)	0	6.7% (0.2, 31.9)
Skin Rash		0.9% (0.0, 1.8)	0.7% (0.0, 2.1)	2.0% (0.0, 4.8)	0
Swelling		7.8% (5.8, 10.2)	6.4% (2.3, 10.4)	7.2% (2.1, 12.4)	0
Trauma		0	0.7% (0.0, 2.1)[6]	0	0
Wrinkling		0.7% (0.0, 1.5)	3.9% (0.5, 7.3)	6.0% (0.8, 11.2)	6.7% (0.2, 31.9)

[1] Includes reports of only ≥ moderate severity for all complications except for reoperation, implant removal, implant extrusion, implant rupture, and pneumothorax.
[2] 184 primary augmentation patients experienced at least one complication.
[3] 80 revision-augmentation patients experienced at least one complication.
[4] 56 primary reconstruction patients experienced at least one complication.
[5] 9 revision-reconstruction patients experienced at least one complication.
[6] 1 case of herniation post-auto accident.

D. Main Reasons for Reoperation

Table 6 below shows the main reasons for reoperations, stratified by indication, through 4 years. The rates are based on the total number of reoperations for that indication.

Table 6: Main Reasons for Reoperations through 4 Years

Reasons for Reoperation through 4 Years[1]	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
	N=135 Reops in 103 Patients	N=83 Reops in 49 Patients	N=54 Reops in 39 Patients	N=7 Reops in 5 Patients
Asymmetry	5 (3.7%)	3 (3.6%)	8 (14.8%)	0
Biopsy	12 (8.9%)	8 (9.6%)	3 (5.6%)	0
Breast cancer	1 (0.7%)	2 (2.4%)	0	0
Breast pain	1 (0.7%)	1 (1.2%)	0	0
Capsular contracture III/IV	39 (28.9%)	14 (16.9%)	10 (18.5%)	1 (14.3%)
Delayed wound healing	3 (2.2%)	3 (3.6%)	1 (1.9%)	0
Hematoma/seroma	9 (6.7%)	11 (13.3%)	6 (11.1%)	0
Implant extrusion	1 (0.7%)	2 (2.4%)	2 (3.7%)	0
Implant malposition	21 (15.6%)	6 (7.2%)	12 (22.2%)	0
Implant palpability/visibility	0	1 (1.2%)	0	0
Implant rupture (suspected)[2]	6 (4.4%)	4 (4.8%)	1 (1.9%)	0
Infection	1 (0.7%)	2 (2.4%)	0	0
Necrosis	1 (0.7%)	0	1 (1.9%)	0
Nipple complications (unplanned)	1 (0.7%)	3 (3.6%)	0	4 (57.1%)
Patient request for style/size change	7 (5.2%)	3 (3.6%)	2 (3.7%)	0
Ptosis	19 (14.1%)	9 (10.8%)	3 (5.6%)	0
Scarring/hypertrophic scarring	8 (5.9%)	8 (9.6%)	3 (5.6%)	2 (28.6%)
Wrinkling	0	1 (1.2%)	0	0
Breast tissue contour deformity	0	1 (1.2%)	2 (3.7%)	0
Iatrogenic/traumatic injury	0	1 (1.2%)	0	0

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

[2] Primary Augmentation - Three devices were removed and found to be intact, and the other devices were confirmed to be ruptured. Revision-Augmentation – Three devices were removed and found to be intact, and the other device was confirmed to be ruptured. Primary Reconstruction - The device was removed and found to be intact.

E. Main Reasons for Implant Removal

Table 7 below shows the main reasons for removal, stratified by indication, through 4 years. There were no implant removals for revision-reconstruction patients. The rates are based on the total number of explantations for that indication.

Table 7: Main Reasons for Implant Removal through 4 Years

Reasons for Implant Removal through 4 Years[1]	Primary Augmentation	Revision-Augmentation	Primary Reconstruction
	N=77 Explants in 41 Patients	N=32 Explants in 18 Patients	N=28 Explants in 23 Patients
Asymmetry	5 (6.5%)	1 (3.1%)	4 (14.3%)
Breast cancer	1 (1.3%)	1 (3.1%)	0
Breast pain	2 (2.6%)	1 (3.1%)	0
Capsular contracture III/IV	27 (35.1%)	9 (28.1%)	7 (25.0%)
Hematoma/seroma	1 (1.3%)	0	2 (7.1%)
Implant extrusion	1 (1.3%)	0	1 (3.6%)
Implant malposition	9 (11.7%)	5 (15.6%)	8 (28.6%)
Implant rupture (suspected)[2]	7 (9.1%)	4 (12.5%)	1 (3.6%)
Infection	0	1 (3.1%)	0
Necrosis	0	0	1 (3.6%)
Patient request for style/size change	18 (23.4%)	6 (18.8%)	4 (14.3%)
Ptosis	6 (7.8%)	2 (6.3%)	0
Scarring/hypertrophic scarring	0	2 (6.3%)	0

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

[2] Primary Augmentation - Three devices were removed and found to be intact, and the other devices were confirmed to be ruptured. Revision-Augmentation – Three devices were removed and found to be intact, and the other device was confirmed to be ruptured. Primary Reconstruction - The device was removed and found to be intact.

F. Other Clinical Safety Outcomes

Below is a summary of clinical findings from the Allergan Core Study with regard to connective tissue disease (CTD), CTD signs and symptoms, cancer, lactation complications, reproduction complications, and suicide. These issues, along with others, will be further evaluated beyond 4 years as part of an Allergan postapproval study of a large number of patients followed through 10 years.

CTD Diagnoses

Two primary augmentation patients (0.4%) were reported to have a new diagnosis of rheumatoid arthritis according to a rheumatologist at 7 months and at 3 years after implantation in the Allergan Core Study. One revision-augmentation patient (0.7%) was reported to have a new diagnosis of fibromyalgia at 10 months after implantation. There was one primary reconstruction patient (1%) in the Allergan Core Study who was reported to have a new diagnosis of systemic sclerosis/scleroderma according to a rheumatologist at 3 months after implantation. No revision-reconstruction patients had new diagnoses of a CTD

through 4 years. It cannot be concluded that these CTD diagnoses were or were not caused by the implants because there was no comparison group of similar women without implants.

CTD Signs and Symptoms

In Allergan's Core Study, numerous signs and symptoms were collected. For primary augmentation patients at 4 years after implantation, statistically significant increases were found for the symptom category of Pain (which includes muscle pain, aches, and cramps). No significant increases were found in the categories of General, Joint, Muscular, Skin, Gastrointestinal, Neurological, Urinary, Fatigue, Fibromyalgia, and Other. For revision-augmentation patients at 4 years after implantation, no statistically significant increases were found in any of the symptom categories.

For primary reconstruction patients at 4 years after implantation, statistically significant increases were found for the symptom categories of Gastrointestinal (which includes constipation, diarrhea, gastrointestinal pain, heartburn, loss of appetite, nausea, stomach pain or cramps and vomiting) and Fibromyalgia symptoms (including fatigue, non-specified pain, back pain, neck pain and chest pain). No significant increases were found in the categories of General, Joint, Muscular, Skin, Neurological, Urinary, Fatigue, Pain, and Other. For revision-reconstruction patients at 4 years after implantation, no statistically significant increases were found in any of the symptom categories.

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

Cancer

There was 1 primary augmentation patient with a new diagnosis of breast cancer through 4 years in the Allergan Core Study. There was a 10% benign breast disease rate and 1% unknown breast disease (not yet diagnosed) rate through 4 years. For revision-augmentation patients, there were no reports of new diagnoses or reoccurrence of breast cancer or unknown breast disease and a 10% benign breast disease rate through 4 years. In primary augmentation patients there was 1 report of thyroid cancer and 1 report of brain cancer. There were no reports of other cancers, such as respiratory or cervical/vulvar, in revision-augmentation patients.

There were 7 primary reconstruction patients (7%) with reoccurrence of breast cancer through 4 years in the Allergan Core Study. There was a 12% benign breast disease rate through 4 years. For revision-reconstruction patients, there were no reports of new diagnoses or reoccurrence of breast cancer and a 13% benign breast disease rate through 4 years. There were no reports of other cancers, such as brain, respiratory, or cervical/vulvar, in primary reconstruction or revision-reconstruction patients.

Lactation Complications

Nine (18%) of the 51 primary augmentation patients who attempted to breast feed following breast implantation in the Allergan Core Study through 4 years experienced difficulty with breast feeding. The most common difficulty was inadequate milk production. For the 13

revision-augmentation patients who attempted to breast feed, 2 (15%) had difficulty breast feeding, 1 due to inadequate milk production and 1 due to pain. One of the 98 primary reconstruction patients in the Allergan Core Study attempted to breast feed through 4 years and did not experience any difficulties. No revision-reconstruction patients attempted to breast feed after receiving breast implants.

Reproduction Complications

Nineteen (4%) of the primary augmentation patients in the Allergan Core Study reported a reproduction problem through 4 years, most commonly miscarriage. For the 5 (3%) revision-augmentation patients who experienced a reproduction problem through 4 years, the most common problem was infertility. Two (2%) of the primary reconstruction patients in the Allergan Core Study reported a reproduction problem through 4 years. No revision-reconstruction patients experienced a post-implantation reproduction problem.

Suicide

There were 2 reports of suicide in the revision-augmentation patients in the Allergan Core Study, and no reports of suicide in the primary augmentation, primary reconstruction, and revision-reconstruction patients through 4 years.

G. Effectiveness Outcomes for Core Study

Effectiveness was assessed by cup/circumferential chest size measurements, patient satisfaction, and QoL. Allergan's patient satisfaction was based on a 5-point scale assessment of satisfaction with their implants at the time of the follow-up visits. The QoL measures were the Rosenberg Self Esteem Scale, the Body Esteem Scale, the Tennessee Self Concept Scale, and the SF-36.

Primary Augmentation Patients

For primary augmentation patients, 396 (87%) of the original 455 patients had a breast measurement within 18 months of surgery. Of these 396 patients, 41% increased by 1 cup size; 45% increased by 2 cup sizes; 8% increased by more than 2 cup sizes; and 6% had no increase or decrease due to correction of congenital asymmetry or change in shape without change in size.

Of the original 455 patients, 364 (80%) provided a satisfaction rating at 4 years after implantation. Of these 364 patients, 346 (95%) indicated that they were satisfied with their breast implants.

The SF-36 showed a slight improvement in one scale and a slight worsening in another scale after 4 years compared to before breast implantation, although all scales remained higher than the general U.S. female population. For patient responses to questions regarding overall self-concept/self-esteem, there was a decrease in self-concept on the Tennessee Self Concept Scale and no change in overall self esteem on the Rosenberg Self Esteem Scale 4 years after receiving implants. Patient responses to questions on the Body Esteem Scale regarding overall body image did not show a change 4 years after receiving implants, but body esteem related to sexual attractiveness did show an increase in primary augmentation patients.

Revision-Augmentation Patients
Revision-augmentation patients did not undergo a measurement of breast cup size change because they were undergoing replacement of an existing breast implant.

Of the original 147 revision-augmentation patients, 111 (76%) provided a satisfaction rating at 4 years. Of these 111 patients, 96 (87%) indicated that they were satisfied with their breast implants.

The SF-36 showed changes in these scales after 4 years. Patient responses to questions on the Tennessee Self Concept Scale, Rosenberg Self Esteem Scale, and Body Esteem Scale regarding overall self-concept/self-esteem and body image showed no changes 4 years after receiving implants.

Primary Reconstruction Patients
Of the original 98 primary reconstruction patients, 67 (68%) provided a satisfaction rating at 4 years after implantation. Of these 67 patients, 63 (94%) indicated that they were satisfied with their breast implants.

The SF-36 showed no changes after 4 years compared to before breast implantation. For patient responses to questions regarding overall self-concept/self-esteem, there was no change in self-concept on the Tennessee Self Concept Scale and no change in overall self esteem on the Rosenberg Self Esteem Scale 4 years after receiving implants. Patient responses to questions on the Body Esteem Scale regarding overall body image also did not show a change 4 years after receiving implants.

Revision-Reconstruction Patients
Of the original 15 revision-reconstruction patients, 13 (87%) provided a satisfaction rating. Of these 13 patients, 12 (92%) indicated that they were satisfied with their breast implants.

Responses were similar pre- and post-implantation on the SF-36, Tennessee Self Concept Scale, Rosenberg Self Esteem Scale, and Body Esteem Scale.

XI. RUPTURE RATE AND CONSEQUENCES OF RUPTURE

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

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

A. Allergan Core Study

While Section X above provided the rupture rates, this section includes additional details regarding rupture in the Allergan Core Study. Allergan's Core Study included rupture rate data from the MRI cohort (original sample size of 264 who had scheduled MRIs to screen for silent rupture) at years 1 and 3 and from the non-MRI cohort (original sample size of 451) at years 1, 2, 3, and 4. The reported ruptures were from patients in both the MRI and non-MRI cohorts. The rupture rates in the MRI cohorts were 2.7% for primary augmentation, 4.0% for revision-augmentation, 0% for primary reconstruction, and 0% for revision-reconstruction through 4 years. For the non-MRI cohort, rupture was reported in 1 primary augmentation, 1 revision-augmentation, 0 primary reconstruction, and 1 revision-reconstruction patient. There were a total of 9 ruptured/suspected ruptured implants in 9 patients through 4 years, from patients in both the MRI and non-MRI cohorts. Five of these implants were explanted and confirmed to be ruptured; the remaining 4 were considered ruptured based on physical or MRI evaluation. All 9 ruptured/suspected ruptured implants showed intracapsular gel, and one intracapsular gel progressed into extracapsular gel following exploratory surgery to confirm the rupture and then implant replacement was delayed. There were no cases of migrated gel.

In summary, the Allergan Core Study, which was the primary source of rupture rate data for the Allergan product, provided compelling data demonstrating low rates of rupture through 4 years.

B. International MRI Study

Allergan submitted the International MRI Study[9], a European study, to provide information characterizing the rupture rate over a longer period of time than had been evaluated in the Core Study, as well as to provide supplemental information on the consequences of rupture. Excluding 5 patients with Style 153 implants, silent rupture data were collected via a single MRI on 106 patients (77 augmentation, 11 reconstruction, and 18 revision). The average age of the implants was 11 years. Silent rupture was found in approximately 15% of the combined group of augmentation, reconstruction, and revision patients. There was one possible case of extracapsular rupture, with the remainder of the cases classified as intracapsular ruptures. No cases of migrated gel were found.

FDA acknowledges that the International MRI Study is of limited value in providing a precise estimate of the long-term rupture rate. However, using the same framework discussed by the April 2005 Panel in assessing rupture, we determined that this study, which involved the specific devices for which approval was sought, provided valuable information to help characterize the long-term rupture rate and consequences of rupture. The study showed a relatively low rate of rupture at an average of 11 years for the women in the study. As with the Allergan Core Study, the low rates of rupture limited our ability to assess the consequences of rupture. However, the data we do have suggest that, when rupture does occur, gel migration is unlikely.

C. Allergan Adjunct Study

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

D. Literature

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

Studies of Danish women evaluated with MRI involving a variety of manufacturers and implant models showed that about three-fourths of implant ruptures are intracapsular and the remaining one-fourth is extracapsular.[10] Additional studies of Danish women indicate that over a 2-year period, about 10% of the implants with intracapsular rupture progressed to extracapsular rupture as detected by MRI.[11] This means that for women with silicone gel rupture within the scar tissue capsule detected via MRI after 2 years, 1 in 10 of these women had progression of the gel outside the scar tissue capsule. Approximately half of the women whose ruptures had progressed from intracapsular to extracapsular reported that they experienced trauma to the affected breast during this time period or had undergone mammography. In the other half, no cause was given. In the women with extracapsular rupture, after 2 years, the amount of silicone seepage outside the scar tissue capsule increased for about 14% of the women. This means that for 100 women with silicone gel rupture outside the scar tissue capsule, the amount of gel outside the scar tissue capsule increased for 14 women 2 years later. This type of information pertains to a variety of silicone implants from a variety of manufacturers and implant models, and it is not specific to Allergan's implants.

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

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

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

- Concerns have been raised over whether ruptured implants are associated with the development of connective tissue or rheumatic diseases and/or symptoms such as fatigue and fibromyalgia.[12,13,14,15] A number of epidemiology studies have evaluated large populations of women with breast implants from a variety of manufacturers and implant models.",[16,17,18,19,20,21] However, other than one small study, these studies do not distinguish whether the women had ruptured or intact implants. These studies do not, taken together, support an association of breast implants with a typical, diagnosed rheumatic disease.

E. Retrieval Study and Fatigue Testing

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

Allergan used the raw data from their fatigue testing in a mathematical model that adjusted for the load/stress from walking, jogging, running, lying face down, and shell wrinkling. The results from this model demonstrated that the devices can withstand lengthy cyclic loading for decades without failure due to inherent design or material flaws.

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

XII. SUMMARY OF OTHER CLINICAL INFORMATION

The literature was also used to assess:

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

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

The Danish Breast Implant Registry was intended to provide additional information to characterize longer-term rupture rates and health consequences of rupture. The registry involved 263 Allergan devices, with a median in-vivo duration of approximately 3.8 years, for which no ruptures were reported. There were no new safety issues raised by these data; however, based on the lack of MRI screening, FDA reviewed these data in the context of providing only supporting information rather than defining the long-term rupture rate for Allergan's product.

XIII. PANEL RECOMMENDATION

The Allergan PMA was presented at two separate advisory meetings.

At the first advisory meeting held on October 14-15, 2003, the General and Plastic Surgery Advisory Panel recommended, in a 9 to 6 vote, that Allergan's PMA for the Inamed® Silicone-Filled Breast Implants be approved subject to the specific conditions.[‡] However, subsequent to the October 2003 Panel meeting, FDA determined that the PMA was not approvable because the data did not provide a reasonable assurance of the safety of the device. Accordingly, FDA issued a not approvable letter to Allergan and a draft updated guidance document in January 2004. The primary issues identified by FDA were the need for additional data to characterize the rupture rate over time, the health consequences of rupture, and the modes and causes of implant rupture. In August 2004, Allergan provided responses to the January 2004 not approvable letter.

At the second advisory meeting held on April 11-13, 2005, the General and Plastic Surgery Advisory Panel recommended, in a 5 to 4 vote, that Allergan's PMA be not approved. Some of the issues cited were: lack of long term data to characterize rupture rate (2 MRI data points and no silent rupture data past 3 years); issues with Style 153 (shown by Allergan's stratified rupture data and modes and causes of rupture); issues with gel bleed testing; issues with modes/causes of rupture studies; and CTD analysis issues. However, subsequent to the April 2005 Panel meeting, Allergan removed Style 153 from consideration in the PMA, and provided a reanalysis of Core Study data after removal of Style 153 data, an International MRI Study, revised retrieval study report after removal of Style 153 data, an updated GEE analysis of the CTD signs and symptoms data, a new lifetime estimate based on cyclic fatigue data, and a new gel bleed testing protocol and results.

XIV. CDRH DECISION

Allergan provided additional information to address the April 2005 Panel issues, and FDA issued a letter to Allergan on September 20, 2005, advising that its PMA was approvable subject to Allergan addressing issues related to postapproval conditions and labeling. The issues identified by FDA included revising the indications for use to limit augmentation to women who were at least 22 years old, stratifying the revision data into revision-augmentation

[‡] The recommended conditions of approval from the October 2003 Panel for Allergan's PMA were similar to the recommended conditions of approval from the April 2005 Panel meeting for a competitor's PMA.

and revision-reconstruction indications, providing a report of the results of new gel bleed testing, providing clarification on some of the Core Study data, establishing a recommendation for the method and frequency of screening for silent rupture, modifying the physician labeling, modifying the patient labeling, developing a patient informed decision process, revising the Core postapproval study protocol, revising the physician training program, and describing their plans for a postapproval registry. Allergan submitted a response to the approvable letter in November 2005, after which FDA continued to develop the postapproval plans and labeling with the sponsor.

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

FDA followed the April 2005 Panel's recommendation regarding:

- continuation of the Core Study; however, the study has been modified to require MRIs every 2 years on all patients and to collect data on patients who had their device(s) removed
- continued follow-up of currently-enrolled Adjunct Study patients through 5 years with no new enrollment
- focus group study of patient labeling
- informed decision process
- modified labeling [prior to approval, Allergan was required to modify their labeling: (1) to include a statement that MRI scans should be performed at 3 years and every 2 years, thereafter; (2) to recommend implant removal if silent rupture is detected; and (3) to remind patients about regular mammography screening]
- mandatory tracking
- a physician training program that includes a certification of participation prior to having access to their product
- FDA will update the Panel on the status of the conditions of approval at years 5 and 10, as well as any other time deemed necessary by FDA if significantly new information from the postapproval studies becomes available.

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

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

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

1. Allergan must continue their Core Study until all patients have completed their 10-year evaluation in order to assess the long-term clinical performance of their product. Data are to be collected via annual physician follow-up evaluations. The primary changes to the protocol from premarket to postapproval are that all non-MRI patients will have a MRI at years 7 and 9 and that all patients who were explanted without replacement will be evaluated through 10 years, as per the protocol. Allergan must also update their patient and physician labeling to reflect 5 and 10-year Core Study findings, as well as any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

2. Allergan must conduct the 10-year large postapproval study, as per the protocol that was submitted to FDA on October 16, 2006. This study, which will begin patient enrollment within 90 days after PMA approval, will be a separate study from the Core Study and will include 39,390 Allergan silicone gel patients and 19,605 saline-filled breast implant patients as the control group. The purpose of this study is to address specific issues for which the Core Study was not designed to fully answer, as well as to provide a real-world assessment of some endpoints. The endpoints in the large postapproval study include long-term local complications, connective tissue disease (CTD), CTD signs and symptoms, neurological disease, neurological signs and symptoms, offspring issues, reproductive issues, lactation issues, cancer, suicide, mammography issues, and MRI compliance and rupture results. Data are to be collected via annual patient questionnaires, either completed via the web, mail, or telephone. There will also be physician evaluations at years 1, 4, and 10 to collect local complication data. Allergan must update their patient and physician labeling to reflect 5 and 10-year large postapproval study findings, as well as any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

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

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

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

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

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

5. As part of their formal informed decision process, Allergan must distribute their approved Patient Planner, which will serve as a collective source of information (including the patient labeling) for the patient. Both the physician and the patient are intended to sign designated sections in order to best assure that a patient has obtained the labeling in an adequate enough time prior to surgery to read it and has understood the risks and other information associated with the Allergan device. Allergan must administer their approved survey to a random selection of 50 physicians on an annual basis to determine the success of this process and provide a summary of the survey findings to FDA. FDA will inform Allergan when a survey summary is no longer necessary. In addition, Allergan is to provide training on this process as part of their physician training program.

6. The Allergan Adjunct Study (P910044) was designed to serve a public health need for reconstruction and revision patients. Because the public health need does not exist upon approval of this PMA P020056, Allergan is required to: (1) cease new patient enrollment into the Allergan Adjunct Study and (2) continue the follow-up of all currently-enrolled Allergan Adjunct Study patients through 5 years. These data are to be reported as part of the annual PMA reports for P020056.

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

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

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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