SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Silicone Gel-Filled Breast Implants
Device Trade Name:	Sientra Silicone Gel Breast Implants
Applicant's Name and Address:	Sientra, Inc. 6769 Hollister Ave, Suite 201 Santa Barbara, California 93117
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P070004
Date of FDA Notice of Approval:	March 9, 2012
Expedited:	Not Applicable

II. INDICATIONS FOR USE

The Sientra Silicone Gel Breast Implants are indicated for patients in the following uses (procedures):

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

III. CONTRAINDICATIONS

Breast implant surgery should not be performed in women:

- With active infections anywhere in their body,
- With existing cancer or precancerous conditions who have not received adequate treatment for those conditions, or
- Who are currently pregnant or nursing.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Sientra Silicone Gel Breast Implants labeling.

V. DEVICE DESCRIPTION

Each Sientra Silicone Gel Breast Implant is composed of a silicone elastomer shell, which is thin and soft, and a filler made of clear, high-strength silicone gel. The silicone elastomer used in the implant shell is composed of a compound of dimethyl polysiloxane and a dimethyl fluoro silicone copolymer, catalyzed by a platinum compound. The gel filler is high-strength silicone gel catalyzed by a platinum-containing compound. The implants are sterilized by dry heat and have a 5-year shelf-life from the date of sterilization. The Implants are available in a range of shapes, profiles (projections), and sizes, as well as in smooth and textured shell surfaces.

Table 1 shows the styles that are approved for use by FDA. Table 2 shows the general device material for the shell, patch, and gel components.

Style Number	Shell Surface	Shape and Profile	Size Range (cc)
10512-MP	Smooth	Round Moderate	80-700
10521-HP	Smooth	Round High	95-695
20610-LP	Textured	Round Low	60-700
20621-MP/HP	Textured	Round Moderate/High	95-695
20645-LP	Textured	Shaped Inferior Pole Low	170-500
20645-MP/HP	Textured	Shaped Inferior Pole Moderate/High	120-700
20646-RB	Textured	Shaped Inferior Pole High	180-550
20676-E	Textured	Shaped Superior Pole	115-690

Table 1: Approved Sientra Silicone Gel Breast Implants

Component	Raw Material
Shell, inner/outer layers	High strength silicone elastomer
Shell, barrier layer	Fluorosilicone elastomer
Spherical cap	Liquid silicone rubber
Patch sheeting	High strength silicone elastomer Fluorosilicone elastomer High consistency rubber
Silicone gel filler	High strength silicone gel
Titanium dioxide pigmented silicone ink	Liquid silicone rubber
Position indicator	High consistency rubber Titanium dioxide

Table 2: Device Materials

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the augmentation or reconstruction of the breast with silicone filled breast implants. Alternative procedures include saline-filled breast implant surgery, external prostheses, autogenous tissue grafts, tissue-flap surgeries (e.g., transverse rectus abdominus muscle, latissimus dorsi muscle, gluteal muscle), or no treatment. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Silimed Industria de Implantes, Ltda. (hereinafter called "Silimed-Brazil"), the company that manufactures the Implants for Sientra, is located in Rio de Janeiro, Brazil. Silimed-Brazil began manufacturing its silicone-based medical devices in 1981. To date, Silimed-Brazil has distributed nearly half a million high-strength silicone gel breast implants equivalent or corresponding to the PMA-approved Implants in Europe, South America, Australia, Asia, and Africa. These implants have not been withdrawn from any foreign market for any reason.

In September 2002, Silimed-U.S. received FDA approval to begin its Core Clinical Study for its Silicone Gel Breast Implants. The Core Clinical Study is the primary clinical set in this PMA. In April 2007, Sientra purchased substantially all the assets of Silimed-U.S. and is now the sponsor of the PMA.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- 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
- Lymphadenopathy
- Connective tissue disease (CTD)
- CTD signs and symptoms
- Neurological disease
- Neurological signs and symptoms
- Cancer
- Lymphoma
- Suicide
- Potential effects on offspring.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

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

1. Extent of Cross-linking

Shell – The extent of cross-linking was measured for smooth and textured implant shells. The percent weight gain and crosslink density were uniform over the three lots tested. The physical properties of cured samples of all elastomer lots used for breast implant shells are measured to ensure that they meet or exceed pre-established material specifications for use in the manufacture of the implant shells. This testing demonstrated that the extent of cross-linking of the elastomers used in the shell is sufficient to ensure that shells meet the ASTM F703 [1] specification of a minimum 2.5 lb break force and >350% elongation.

Gel – Using penetrometer testing, every lot of gel is tested to ensure that 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 testing each gel lot used for Implant manufacture. All lots of gel used in the implants have an extent of cross-linking sufficient to achieve the internal specification.

2. Volatiles

Textured implant shells and gel filler were separately tested for volatile organic compounds using EPA test method 8260[2]. Among the three lots tested, only one showed any level of

tetrachloroethylene; this lot showed low levels of tetrachloroethylene (227 ppb in the gel and 174 ppb in the shell). Tetrachloroethylene is the solvent used to disperse the components used to make the implant's shells. No other organic compounds were detected by this method.

3. Extractables

For the exhaustive extraction, components of the device were extracted with different solvents exhaustively. The extracts were analyzed as described below:

Gravimetric analysis: The smooth shell gave 8.97% by weight of extractable tetrahydrofuran residue. The textured shell gave 8.76% by weight of extractable residue. The gel of the smooth shell gave 92.20% by weight of extractable residue. The gel of the textured shell gave 93.09% by weight of extractable residue.

FTIR Analysis: FTIR (Fourier Transform Infra-Red Analysis) was conducted on samples of textured and smooth shell implants. The shells were extracted in three solvents separately. The solvents used were chloroform, methylene chloride, and hexane: methanol (2:1). FTIR was conducted on the shells after extraction. For each extracted sample the FTIR was identical to the one for the as received sample indicating that material extracted is consistent with the silicone polymer comprising the shell. Extract of the shell were also analyzed by FTIR demonstrating the extracts are consistent with PDMS reference spectra.

Gel Permeation Chromatography (GPC): The methylene chloride extractable residue of the shells was taken up in toluene and analyzed by gel permeation chromatograph with a size exclusion column. The system was calibrated using polystyrene standards. The GPC analysis of the residues gave two peaks: (1) an average molecular weight peak at 202,232 and (2) an average molecular weight peak at 12,963. The gel residue was taken up in toluene and analyzed by gel permeation chromatography with an exclusion column. The system was calibrated using polystyrene molecular weight standards. One peak was observed at 8.104E04 for the gel from the smooth shell and 8.242E04 for the gel with the textured shell.

Qualitative and Quantitative Analyses of Shell and Gel Extractables: The residue from the shell and gel extraction was subjected to GC/MS (gas chromatography/mass spectrometry) analysis. The GC/MS was calibrated using D_4, D_5, D_6 and D_9 standard solutions. The results are listed in the table 3 below:

Cyclic Siloxane	**Shell µg/g**	**Gel Filler µg/g**
D_3 (Average)	0.87	ND
D_4	0.60	73
D_5	3.92	510
D_6	25.39	2119
D_7	20.64	2153
D_8	14.01	1560

Cyclic Siloxane	Shell µg/g	Gel Filler µg/g
D_9	8.29	952
D_{10}	6.11	964
D_{11}	5.05	1107
D_{12}	5.76	1111
D_{13}	6.94	1276
D_{14}	9.0	1808
D_{15}	10.93	2180
D_{16}	14.08	2539
D_{17}	18.0	2563
D_{18}	14.84	2471
D_{19}	15.75	2402
D_{20}	21.79	1447
D_{21}	15..24	ND
Sum D_3-D_{21}	**219.45**	**Sum $D_{4\text{-}20}$: 27234**

ND = Not Detected

Table 3: Semi-volatiles Analysis by GC/MS Shell (Chloroform) and Gel Extracts (THF)

There were no solvent residuals detected in the GC/MS analysis.

4. Heavy Metals

Samples of implant shell and gel materials were digested in acid and the metals were analyzed using ICP-Mass Spectroscopy. A small amount of platinum, the catalyst for the curing mechanism, was detected. Complete metal analyses on the individual components of the device are presented in Table 4.

Metal	Shell (ppm)	Gel (ppm)
Antimony	ND	ND
Arsenic	ND	ND
Barium	0.27	ND
Beryllium	ND	ND
Bromine	ND	19
Cadmium	ND	ND
Calcium	ND	ND
Cesium	0.11	ND
Chromium	ND	0.27-0.28
Cobalt	ND	ND
Copper	ND	ND
Germanium	ND	0.07
Iron	ND	ND
Lead	ND	ND
Magnesium	ND	2.8-3.2
Manganese	ND	0.04
Mercury	ND	ND

Metal	Shell (ppm)	Gel (ppm)
Molybdenum	ND	ND
Nickel	ND	0.07-0.08
Phosphorus	4.0	4.7-5.8
Platinum	1.6-1.7	1.1-8.6
Potassium	ND	22
Selenium	ND	ND
Silver	ND	ND
Sodium	ND	ND
Thallium	ND	ND
Tin	0.39-0.95	0.15-0.19
Vanadium	ND	ND
Zinc	ND	0.33-0.37
Zirconium	0.46	ND

ND = Not Detected

Table 4: Heavy Metal Testing Results in µg/g, WCAS Report

Platinum is a metal used as a catalyst in the manufacture of the Shell and Gel Materials of silicone breast implants. The small amounts of platinum remaining in the product may enter the body, either by diffusing through the intact shell (i.e., through gel bleed) or through an implant rupture. FDA has 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 that provides a brief summary of the key scientific studies on platinum and silicone gel-filled breast implants (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM064040).

5. Silica Filler

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

B. Toxicology Data

Sientra provided both pharmacokinetic and biocompatibility testing to address the biological safety of the material used in their device.

Pharmacokinetics

The pharmacokinetics of the implants have been addressed through a risk assessment based on exhaustive solvent extraction data from two different extraction studies conducted on the implants, as well as gel diffusion data. A Margin of Exposure approach was used to assess the safety of one of the compounds released from the device, octamethylcyclotetrasiloxane (D4). Toxicity data are also available for the compounds, decamethylcyclopentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6). The upper-bound estimated dose of D4-D6 received by a patient with two 700 g implants exceeds the provisional (tolerable intake) TI

values or safe levels of exposure for these compounds; however, very conservative estimates were used to estimate dose and to derive the provisional TI values. As a result, it is unlikely that the dose of D4-D6 released from the implants will result in adverse systemic effects in patients with the device.

Biocompatibility Testing

The biocompatibility testing below was conducted for the major device components (shell, gel, finished device) as described in ISO 10993 [3]. The testing demonstrated the biocompatibility of the materials in the Sientra product. Testing conducted is summarized in table 5 below:

Test	Purpose	Acceptance Criteria	Results
1. Cytotoxicity	Extracts of gel and shell materials were evaluated for cytotoxic effects on mouse fibroblast L929 cells.	The test article passed the test if all three monolayers exposed to the test article showed no greater than a grade of 2 (reactivity mild).	The test articles were non-cytotoxic.
2. Irritation &12-Week Muscle Implantation	A 12-week muscular implantation study was conducted in New Zealand White rabbits to evaluate the potential for gel and shell materials to produce local irritation or toxic responses.	Mean macroscopic scores for test implants were compared to mean scores of the control sites. The requirements of the test were met if the difference between test and control score means (macroscopic) was not greater than 1.0.	There were no macroscopic reactions following a 12-week implantation and both test articles were classified as non-irritants. No significant macroscopic reactions were reported for either the shell or gel materials. The mean test score minus the mean control score was 0.0.
3. Acute Systemic Toxicity	Extracts of gel and shell materials were evaluated for acute systemic toxicity. Mice were administered either 50 ml/kg of test article-extract material or a vehicle control (NaCl solution or sesame oil). The NaCl extract was injected by the intravenous route, while the sesame oil extract was injected by the intraperitoneal route. The mice were observed immediately after dosing and at 4, 24, 48, and 72 hours.	If during the observation period, none of the mice treated with the individual test extract exhibited a significantly greater reaction than the corresponding control mice, the test extract met the test requirements.	There was no mortality or evidence of toxicity.

Test	Purpose	Acceptance Criteria	Results
4. Hemocompatibility	The purpose of the test was to determine whether the gel and shell materials would cause hemolysis. Whole blood New Zealand rabbit samples diluted with saline was exposed to the test articles for 3 hours at 37˚C.	An average hemolytic index of the triplicate test samples was compared to the negative control. A hemolytic index of 2% or less was considered to be nonhemolytic.	The mean hemolytic index for all test articles was 0% and the articles were found to be nonhemolytic.
5. Pyrogenicity	The purpose of the test was to evaluate the gel and shell materials for material mediated pyrogenicity. New Zealand White rabbits were given a single intravenous (i.v.) injection via the marginal ear vein with an extract of the test material. Rectal temperatures were measured up to 3 hours post-injection.	If no single animal showed an increase of more than 0.4˚C above its baseline temperature, then the solution was judged non-pyrogenic.	There was no evidence of a pyrogenic response and all recorded temperature rises were within normal limits.
6. Immunotoxicity	The purpose of the study was to assess the effects of the gel and shell materials on immune functions following subcutaneous implantation in female Fischer 344 rats. Rats were subcutaneously implanted with the test articles and observed for 30 days. The parameters of evaluation included histopathology, clinical pathology, T cell-dependent antibody response to sheep red blood cells (SRBC) natural killer cell (NK) activity, phagocytic activity, and immunophenotyping for call surface markers.	Animals were assessed for reactions.	The results showed that there was minimal immunosuppressive impact by the test materials.
7. Sensitization	Sensitization testing was done to evaluate the potential for gel and shell materials to induce delayed dermal contact sensitization in guinea pigs. The test articles were extracted utilizing either 0.9% NaCl (USP) or sesame oil (NF).	Scoring grades of 1 or greater in the test group generally indicated sensitization, provided that grades of less than 1 were observed on the control animals.	There was no evidence of the extracts of the shell or gel material inducing delayed dermal contact sensitization in either study.

Test	Purpose	Acceptance Criteria	Results
8. Reproductive Toxicology and Teratogenicity	A two-generation reproductive/developmental toxicity study was conducted in rats to assess the potential reproductive and developmental toxicity of the gel and shell materials. Potential reproductive effects were assessed through the mating of two generations of rats (parental or F0 and F1). F0 females received either 4 g of silicone gel or 2 g of silicone implant shell material by subcutaneous implantation and were exposed to these materials for 6 weeks prior to mating. Litter endpoints (e.g., litter size, sex ratio, body weights) were assessed in F1 offspring.	Animals were assessed for reactions.	The data indicate that there were no implant-related, adverse effects in F0 females. From a reproductive toxicity perspective, there were no effects on mating or reproductive performance, on precoital interval, or on pup sex ratio. With regard to developmental effects, there were no adverse effects seen in the F1 generation and differences in the onset of sexual maturation were not seen among the F1 offspring. Under the conditions of the test, the results of the study demonstrate that the silicone gel and the silicone-implant shell material do not have adverse effects on reproduction and development in Sprague Dawley rats
9. Genotoxicity - Salmonella Reverse Mutation Assay (Ames Test)	The purpose of this testing was to assess the potential of the finished implant to induce gene mutations.	A test was considered acceptable if for each strain: (1) the bacteria demonstrate their typical responses to crystal violet and ampicillin, (2) the control plates without S9 mix were within acceptable ranges, (3) corresponding background growth on both negative control and test plates, and (4) the positive control showed a distinct enhancement over the control plate.	The test materials did not induce gene mutations by base pair changes or frame shifts in the genome of the strains tested. The test article is considered non-mutagenic in the Salmonella typhimurium reverse mutation assay.

Test	Purpose	Acceptance Criteria	Results
10. Genotoxicity - In Vitro Mammalian Cell Gene Mutation Test (HPRT-LOCUS) in Hamster V79 Cells	The purpose of the test was to assess the potential of the finished implant to induce cell gene mutations in V79 cells of the Chinese Hamster.	A test is considered to be negative if there is no concentration-related increase in the number of mutants.	The extract of the test materials did not induce gene mutations. The test article is considered to be non-mutagenic in this cell gene mutation test.
11. Genotoxicity - In Vitro Mammalian Chromosome Aberration Test in Chinese Hamster V79 Cells	The purpose of the test was to assess the potential of the finished implant to induce structural chromosome aberrations in V79 cells of the Chinese Hamster.	The chromosomal aberration assay is considered acceptable if it meets the following criteria: (1) the number of aberration found in the negative and/or solvent controls falls within the range of historical laboratory control data: 0.00 %-4.50 % , and the positive control substances should produce significant increases in the number of cells with structural chromosome aberrations.	The extract of the test materials did not cause structural chromosome aberrations in the V79 Chinese hamster cell line. The test article is considered to be non-mutagenic in this chromosome aberration test.
12. Genotoxicity-Micronucleus Cytogenetic Assay in Mice	The purpose of the test was to assess the toxicity of corn and saline extracts of the finished device in the micronucleus assay following intraperitoneal administration in ICR mice.	Animals were assessed for reactions.	The extracts of the materials were determined to have no clastogenic activity.
13. Chronic Toxicity and Carcinogenicity	The carcinogenicity of the silicone elastomers and gel used in implant has been evaluated in a 2-year chronic toxicity and carcinogenicity study in female Fischer 344 rats.	Animals were assessed for reactions.	The sterilized, cured elastomer and gel are non-toxic and non-carcinogenic

Table 5: Summary of Toxicology Data

C. Mechanical Data

1. Fatigue Testing

Cyclic fatigue testing of the Silicone Gel Breast Implants was conducted to determine the number of cycles for various loads at which devices fail or rupture and the endurance load at which the devices do not fail. The testing was conducted in air at ambient temperature. Dry heat sterilized finished devices (80 cc smooth round moderate profile and textured round low profile) were tested. The implants were tested in the range of 1-2Hz at various loads to either run out (7 million cycles without rupture) or failure. Prediction intervals for cycles to failure were determined. Regression analysis predicts that smooth implants will achieve run out at greater than 33.0 lb load amplitude and that textured implants will achieve run out at greater than 46.2 lbs. The experimental data confirmed these predictions.

2. Gel Bleed Testing

Intact implants were extraction tested in bovine calf serum to model the natural condition of the breast implant. The extracts were analyzed for the low molecular weight siloxanes (specifically the cyclic siloxanes D4-D21 and the linear siloxanes MD2M-MD19M) using either GC/FID or GC/MS and analyzed for platinum using inductively coupled plasma spectroscopy with mass spectroscopy. The concentrations of the siloxanes in the extracts were compared with those identified in blank samples (serum incubated without an implant). The ranges of concentrations in the extraction samples were not statistically significantly different from those of the blank for the majority of the detectable siloxanes. Only two of the linear siloxanes (MD6M and MD16M) were determined to be significantly different from the blank concentrations. These siloxanes were measured at low levels, with maximum extractable concentrations of 0.6 and 0.01 μg/g implant. The platinum concentration measured in the serum extract was below the limit of detection.

The scientific literature contains case reports of silicone gel migration in women with intact (non-ruptured) breast implants [4, 5] that identified silicone using H-localized spectroscopy in the liver of women with intact silicone gel-filled breast implants. There is no evidence of a health consequence associated with gel diffusion/bleed. Toxicological testing indicates that the silicone material used in Sientra Silicone Gel Breast Implants does not cause toxic reactions in test animals.

3. Gel Cohesion Testing

Gel cohesivity and penetration testing were conducted to assess the cohesive and cure characteristics of silicone gel, respectively. Gel cohesion testing was conducted on final finished product to standard EN 12180:2000[6], and the samples met the requirements of the test. In-process penetrometer measurements of 425 silicone-gel mixtures performed over a 6-month period revealed that gel cohesion was consistent over time.

D. Modes and Causes of Rupture

Sientra provided numerous test reports and other information to characterize modes and causes of failure for its devices for a range of implantation 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 Sientra Retrieval Study evaluated the physical characteristics and mechanical properties of the explants retrieved from the clinical study and analyzed the modes and causes of failure for study implants with failed or ruptured shells. In addition, Sientra analyzed the durability of the study implants to understand any potential correlations between the failed study implants and the conditions of implantation, mechanical properties, and clinical use of the implants over time.

After careful laboratory testing and analysis of 97 retrieved study implants, ten were confirmed as having failed shells. Upon SEM microscopic analysis and comparison with the micrographs from an *Induced Failure Characterization* study characterizing instrument damage, it was determined that eight of the study implants with failed shells were damaged by surgical instruments. Two of the study implants with failed shells had unknown causes of failure; although, one of those implants was shown to have a shell layer separation, which is considered a manufacturing imperfection. However, it remains unknown whether this was the cause of failure.

Analysis of the data from the durability studies showed that instrument damage at the time of surgery is the most common cause of failed-implant shells. The analysis of the potential association between the shell failure and factors that might predict implant failures showed no statistically significant association between the failed shells and any of the factors analyzed. The analysis also found no statistically significant correlation between the duration of implantation and any of the mechanical properties under consideration.

Overall, evaluation and analysis of the implants retrieved from the clinical study showed that the implants do not change significantly during implantation; the shells are robust during implantation and shell damage is primarily caused by surgical instruments. There were no definitive correlations between implant failure and surgical parameters, implant characteristics, or patient variables. Sientra Silicone Gel Breast Implants are robust and durable for their intended use.

E. Shelf Life

Sientra'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). Accelerated and real time test results were used to establish the shelf life of the Sientra Silicone Gel Breast Implant. All device and package testing met the acceptance criteria set in the protocol. The data supported a 5-year shelf life for the Sientra Silicone Gel Breast Implant.

X. SUMMARY OF SIENTRA CLINICAL STUDY

Sientra performed a clinical study to establish a reasonable assurance of safety and effectiveness of breast augmentation, reconstruction and/or revision with Sientra Silicone Gel Breast Implants in the US under IDE #G010193. Data from this clinical study were the basis for the PMA approval decision. The study consists of data from the primary augmentation and revision- augmentation cohorts of the core study, as well as pooled data from Sientra's Core and Continued Access studies for the primary reconstruction and revision-reconstruction cohorts. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between November 11, 2002 and June 23, 2007. The database for this PMA reflected data collected through December 20, 2010. There were 36 investigational sites.

The study is proposed as a 10-year open-label, prospective, multi-center clinical study. It assessed the safety and effectiveness of 1,788 patients implanted with 3,506 Sientra Silicone Gel Implants with at least 3-years of follow-up. There are 1,115 primary augmentation patients and 362 revision-augmentation patients. Of the 229 primary reconstruction patients in the study, 156 patients were from the core study and 73 were from the Continued Access study. Of the 82 revision-reconstruction patients enrolled in the study, 50 were from the core study and 32 were from the Continued Access study.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the study was limited to patients who met the following inclusion criteria:
   - Female
   - Age limitation per indication:
     - Primary/Revision Augmentation: Must be 18 years or older
     - Primary/Revision Reconstruction: No age limit
   - Adequate tissue available to cover implant(s)
   - Willingness to follow study requirements
   - Candidate for primary augmentation, primary reconstruction, or revision as defined below:
     - Primary Augmentation (severe ptosis, general breast enlargement, asymmetry)
     - Primary Reconstruction (post-mastectomy or lumpectomy/surgical removal of breast as a result of cancer or other disease; post-trauma: total or partial removal of breast(s) resulting in significant deformity (for any reason); congenital deformity or acquired discrepancy in breast size including but not limited to, pectus excavatum/carinatum, scoliosis, Poland's Syndrome and tuberous breast; contralateral augmentation mammoplasty as a result of the affected breast requiring surgery, to provide symmetry)

- Revision (women who require replacement of an existing breast implant where medical or surgical reasons exist)

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Advanced fibrocystic disease, considered to be pre-malignant without mastectomy
- Inadequate or unsuitable tissue (e.g., due to radiation damage, ulceration, compromised vascularity, history of compromised wound healing)
- Active infection in the body at the time of surgery
- Pregnant or lactating
- Medical condition such as obesity, diabetes, autoimmune disease, chronic lung or severe cardiovascular disease that might result in unduly high surgical risk and/or significant postoperative complications
- Use of drugs, including any drug that would interfere with blood clotting, that might result in high risk and/or significant postoperative complications
- Demonstrated psychological characteristics that are unrealistic or unreasonable given the risks involved with the surgical procedure
- Determination by physical examination that the subject has any connective tissue/autoimmune disorder, such as systemic lupus erythematosus, discoid lupus or scleroderma
- Existing carcinoma of the breast without accompanying mastectomy
- Magnetic resonance imaging (MRI) scan is prohibited because of implanted metal device, claustrophobia, or other condition

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 6-10 weeks, 1 year, 2 years, and annually through 10 years, postoperatively. Quality of Life assessments occur at baseline and 1, 2, 4, 6, 8 and 10 years. A subgroup of patients was scheduled to have MRIs to screen for silent rupture, beginning at year 3, continuing every other year through 10 years (MRI cohort). Adverse events and complications were recorded at all visits.

Study	Follow-up Schedule
All Participants	6-10 weeks
	1 year
	2 years
	3 years
	4 years
	5 years
	6 years
	7 years
	8 years
	9 years
	10 years
MRI Cohort	Baseline, beginning at 3-years
	Every other year through 10 years

Table 6: Follow-up schedule

3. Clinical Endpoints

The assessment of safety was based on the incidence of patient complications, including device ruptures and adverse device effects. The study collected data to make safety assessments including complication rates, reasons for reoperation, and reasons for implant removal.

The study collected data to support assessments of effectiveness including circumferential chest-size change and bra cup-size change (primary augmentation patients only), patient satisfaction, and quality of life (QOL). QOL was assessed using three different survey tools: one measures self-esteem, one body image, and one measures general health over time.

4. Statistical Analysis Plan

The clinical study data collected was used to produce safety and effectiveness analyses. The risk of occurrence of safety endpoints (complications, reoperations, explantation) were estimated using Kaplan-Meier. Reoperations and explantations were analyzed to provide a frequency distribution of the reasons for the procedures, and a frequency distribution of the various reoperation procedures was produced.

Effectiveness analyses include a comparison of pre-implantation to post-implantation bra/cup sizes, to assess anatomical change. Additionally, responses to the various quality of life scales (SF-36, Rosenberg Self Esteem, and Body Esteem) were tabulated for a comparison analysis between pre-implantation and post-implantation results.

The results through 3 years are reported, although the study remains ongoing. Data will continue to be analyzed and reported to FDA at regular study intervals. In

addition, Sientra will periodically update labeling as more data and information become available.

B. Accountability of PMA Cohort

At the time of database lock, of 1,788 patients enrolled in PMA study, 1,363 (76%) are available for analysis at the 3 year post-operative visit.

1. Augmentation, Reconstruction and Revision Cohorts

The study consists of 1,788 patients (3,506 implants) of which data are available through 3 years. The study is divided into four cohorts including 1,115 primary augmentation patients, 362 revision-augmentation patients. Of the 229 primary reconstruction patients enrolled, 156 patients were from the core study and 73 were from the Continued Access study. Of the 82 revision-reconstruction patients enrolled, 50 were from the core study and 32 were from the Continued Access study. Data through 3 years are available for 80% of the eligible primary augmentation patients, 79% of the eligible revision-augmentation patients, 83% of the eligible primary reconstruction patients, and 76% of the eligible revision-reconstruction patients. Table 7 provides a tabulation of patient accounting.

Follow-up Year	Study Cohort			
	Primary Augmentation	**Revision Augmentation**	**Primary Reconstruction**	**Revision Reconstruction**
Year 1				
Theoretically Due	1115	362	229	82
Discontinued (Deaths & Explants)	4 (0 & 4)	7 (0 & 7)	13 (1 & 12)	6 (0 & 6)
Other Discontinued (Not Avail & Subject Request)	1 (1 & 0)	1 (0 & 1)	2 (0 & 2)	0 (0 & 0)
Expected	1110	354	214	76
Lost to Follow-up	93	37	18	9
Actual Evaluated (% Follow-up)	1017 (92 %)	317 (90 %)	196 (92 %)	67 (88 %)
Year 2				
Theoretically Due	1115	362	229	82
Discontinued (Deaths & Explants)	13 (0 & 13)	15 (1 & 14)	15 (1 & 14)	12 (1 & 11)
Other Discontinued (Not Avail & Subject Request)	3 (1 & 2)	1 (0 & 1)	3 (0 & 3)	0 (0 & 0)
Expected	1099	346	211	70
Lost to Follow-up	173	50	32	9
Actual Evaluated (% Follow-up)	926 (84 %)	296 (86 %)	179 (85 %)	61 (87 %)
Year 3				
Theoretically Due	1115	362	229	82
Discontinued (Deaths & Explants)	21 (0 & 21)	19 (1 & 18)	17 (3 & 14)	14 (2 & 12)
Other Discontinued (Not Avail & Subject Request)	4 (1 & 3)	2 (0 & 2)	3 (0 & 3)	1 (0 & 1)
Expected	1090	341	209	67
Lost to Follow-up	222	71	35	16
Actual Evaluated (% Follow-up)	868 (80 %)	270 (79 %)	174 (83 %)	51 (76 %)

Table 7: Patient Accounting

2. MRI Cohort

Of the 351 patients enrolled in the MRI cohort, 345 (98.3%) underwent their baseline MRI screening. Data on the remaining six patients in the MRI Cohort were incomplete and not available at the time of data lock. Table 8 presents patient accounting for the MRI cohort.

Accounting for Baseline MRI	Patients	
	n	*% Compliance*
Theoretically Due	384	
Discontinued (Death & Explants)	25 (1 & 24)	
Other Discontinued (Claustrophobic)	8	
Expected	351	
Seen	345	98.3%

Table 8: Patient accounting – MRI Cohort

C. Study Population Demographics and Baseline Parameters

Over 90% of the study patients in all four cohorts are Caucasian. The median age at surgery is 36 years for primary augmentation patients, 42 years for revision-augmentation patients, 46 years for primary reconstruction patients, and 50 years for revision- reconstruction patients. Approximately 59% of the study patients are married. Approximately 74% of the study patients have at least some college education. Table 9 below presents the study population demographics at baseline by cohort:

Characteristic	Primary Augmentation N=1115	Revision-Augmentation N=362	Primary Reconstruction N=229	Revision-Reconstruction N=82
Age (years)				
≤ 21	47 (4.2 %)	3 (0.8 %)	8 (3.5 %)	0 (0%)
22-25	102 (9.1 %)	12 (3.3 %)	5 (2.2 %)	0 (0%)
26-39	565 (50.7 %)	127 (35.1 %)	57 (24.9 %)	8 (9.8 %)
40-49	334 (30.0 %)	139 (38.4 %)	67 (29.3 %)	26 (31.7 %)
50-59	58 (5.2 %)	63 (17.4 %)	63 (27.5 %)	28 (34.1 %)
60-69	8 (0.7 %)	18 (5.0 %)	17 (7.4 %)	14 (17.1 %)
70 & over	1 (0.1 %)	0 (0%)	11 (4.8 %)	6 (7.3 %)
Not provided	0 (0%)	0 (0%)	1 (0.4 %)	0 (0%)
Median Age	36 years	42 years	46 years	50 years
Marital Status				
Single	317 (28.4 %)	91 (25.1 %)	48 (21.0 %)	14 (17.1 %)
Married	640 (57.4 %)	217 (59.9 %)	145 (63.3 %)	57 (69.5 %)
Widowed	9 (0.8 %)	9 (2.5 %)	6 (2.6 %)	5 (6.1 %)
Divorced	126 (11.3 %)	42 (11.6 %)	26 (11.4 %)	6 (7.3 %)
Separated	21 (1.9 %)	3 (0.8 %)	1 (0.4 %)	0 (0%)
Not Provided	2 (0.2 %)	0 (0%)	3 (1.3 %)	0 (0%)

Characteristic	Primary Augmentation N=1115	Revision-Augmentation N=362	Primary Reconstruction N=229	Revision-Reconstruction N=82
Race				
Caucasian	1013 (90.9 %)	337 (93.1 %)	208 (90.8 %)	78 (95.1 %)
Black	12 (1.1 %)	7 (1.9 %)	5 (2.2 %)	2 (2.4 %)
Hispanic	37 (3.3 %)	7 (1.9 %)	10(4.4 %)	1 (1.2 %)
Asian	29 (2.6 %)	8 (2.2 %)	1 (0.4 %)	0 (0%)
Indian	1 (0.1 %)	0 (0%)	1 (0.4 %)	0 (0%)
Other	22 (2.0 %)	2 (0.6 %)	2 (0.9 %)	1 (1.2 %)
Not Provided	1 (0.1%)	1 (0.3 %)	2 (0.9 %)	0 (0%)
Education				
Less than 12 years	8 (0.7%)	4 (1.1%)	5 (2.2%)	1 (1.2%)
High School Graduate	187 (16.8%)	68 (18.8%)	72 (31.4%)	23 (28.0%)
Some College	368 (33.0%)	94 (26.0%)	53 (23.1%)	24 (29.3%)
College Graduate	398 (35.7%)	150 (41.4%)	63 (27.5%)	21 (25.6%)
Post Graduate	94 (8.4%)	26 (7.2%)	18 (7.9%)	6 (7.3%)
Not Provided	60 (5.4%)	20 (5.5%)	18 (7.9%)	7 (8.5%)

Table 9: Patient Demographics By Cohort

The following two tables represent implant placement by cohort (Table 10) and breast implant style by cohort (Table 11).

For primary augmentation patients, the most common placement location (57%) was submuscular. Round implants represented 89% of implants used. Smooth implants represented 58% of the implants used and textured implants represented 42%.

For revision-augmentation patients, the most common placement (61%) was submuscular. Round implants represented 86% of implants used. Smooth implants represented 47% of implants and textured implants represented 53% of implants.

For primary reconstruction patients, the most common placement (73%) was submuscular. Round implants represented 88% of implants used. Smooth implants represented 47% of implants and textured implants represented 53% of implants.

For revision-reconstruction patients, the most common placement (90%) was submuscular. Round implants represented 87% of implants used. Smooth implants represented 39% of implants and textured implants represented 61% of implants.

Implant Placement	Primary Augmentation N=2228	Revision-Augmentation N=723	Primary Reconstruction N=420	Revision-Reconstruction N=135
Submuscular	1271 (57.0%)	438 (60.6%)	308 (73.3%)	121 (89.6%)
Subglandular	957 (43.0%)	285 (39.4%)	112 (26.7%)	12 (8.9%)
Other	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)*

*Subcutaneous mastectomy bilateral.

Table 10: Breast Implant Placement By Cohort

Product Style	Primary Augmentation N=2228	Revision-Augmentation N=723	Primary Reconstruction N=420	Revision-Reconstruction N=135
Round				
Style 10512 (Smooth)	716 (32.1%)	136 (18.8%)	82 (19.5%)	17 (12.6%)
Style 10521 (Smooth)	570 (25.6%)	202 (27.9%)	116 (27.6%)	35 (25.9%)
Style 20610 (Textured)	99 (4.4%)	36 (5.0%)	28 (6.7%)	3 (2.2%)
Style 20621 (Textured)	587 (26.3%)	248 (34.3%)	143 (34.0%)	63 (46.7%)
Shaped				
Style 20644 (Textured)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)
Style 20645 (Textured)	54 (2.4%)	12 (1.7%)	9 (2.1%)	11 (8.1%)
Style 20646 (Textured)	0 (0%)	0 (0%)	1 (0.2%)	3 (2.2%)
Style 20676 (Textured)	202 (9.1%)	89 (12.3%)	40 (9.5%)	3 (2.2%)

Table 11: Breast Implant Style by Cohort

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Core study of 1,788 patients available for the 3 year evaluation. The key safety outcomes for this study are presented below in tables 12 to 15.

a. Complication Rates

Table 12 shows the 3-year, by-patient, Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of complications for all four study cohorts. As shown in Table 12, the most common complications through 3 years in the primary augmentation cohort were reoperation (12.6%) and Baker Grade III/ IV capsular contracture (6.0%). The most common complications for the revision-augmentation, primary reconstruction and revision-reconstruction cohorts were reoperation (20.3%, 34.9% and 42.5%, respectively) and implant removal with or without replacement (11.4%, 24.8% and 30.3%, respectively).

KM Rates Through 3 Years	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
	N=1,115 patients	N=362 patients	N=229 patients	N=82 patients
Any complication (including reoperation)	20.2% (17.9, 22.9)	26.3% (21.8, 31.4)	44.6% (38.1, 51.5)	43.2% (32.8, 55.4)
Any reoperation	12.6% (10.7, 14.8)	20.3% (16.3, 25.0)	34.9% (28.9, 41.8)	42.5% (32.0, 54.8)
Implant removal with or without replacement	5.8% (4.5, 7.5)	11.4% (8.4, 15.4)	24.8% (19.5, 31.3)	30.3% (21.0, 42.4)
Any cosmetic complication	10.1% (8.4, 12.1)	17.1% (13.4, 21.7)	29.7% (23.9, 36.5)	33.7% (24.0, 46.1)
Any non-cosmetic (including re-operation)	15.0% (12.9, 17.4)	16.1% (12.5, 20.6)	29.3% (23.5, 36.2)	24.9% (16.1, 37.2)
Asymmetry	1.1% (0.6, 2.0)	1.8% (0.8, 4.0)	8.7% (5.5, 13.7)	7.1% (3.0, 16.2)
Breast mass/cyst/lump	0.3% (0.1, 1.0)	0%	1.0% (0.3, 4.0)	3.1% (0.8, 11.9)
Breast pain	0.8% (0.4, 1.6)	0.9% (0.3, 2.9)	2.6% (1.1, 6.1)	1.4% (0.2, 9.3)

KM Rates Through 3 Years		Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
		N=1,115 patients	N=362 patients	N=229 patients	N=82 patients
Bruising		0.1% (0.0, 0.7)	0.3% (0.0, 2.0)	0.4% (0.1, 3.1)	0%
Capsular contracture (Baker Grade III/IV)		6.0% (4.7, 7.7)	5.2% (3.2, 8.4)	8.8% (5.5, 13.8)	6.8% (2.9, 15.7)
Capsule calcification		0%	0%	0%	0%
Delayed wound healing		0.2% (0.1, 0.7)	0.6% (0.1, 2.3)	1.9% (0.7, 5.0)	0%
Hematoma		0.8% (0.4, 1.6)	0.9% (0.3, 2.6)	0.4% (0.1, 3.1)	0%
Hypertrophic/abnormal scarring		0.6% (0.3, 1.3)	0.7% (0.2, 2.7)	2.7% (1.1, 6.3)	3.1% (0.8, 11.8)
Implant extrusion		0.1% (0.0, 0.8)	0.6% (0.2, 2.3)	1.5% (0.5, 4.5)	0%
Implant malposition		1.2% (0.7, 2.1)	3.2% (1.7, 5.9)	3.0% (1.4, 6.6)	5.5% (2.1, 14.1)
Implant palpability		0%	0.3% (0.0, 2.1)	0.5% (0.1, 3.1)	0%
Implant visibility		0.2% (0.1, 0.9)	0.6% (0.2, 2.3)	1.0% (0.3, 4.1)	0%
Implant rupture	MRI Cohort	2.5% (1.1, 5.5)	0%	0%	0%
	Non-MRI cohort	0%	0.4% (0.1, 2.9)	0%	0%
Infection		0.7% (0.3, 1.5)	1.2% (0.4, 3.1)	5.1% (2.8, 9.0)	1.2% (0.2, 8.4)
Irritation		0%	0.4% (0.1, 2.6)	0.4% (0.1, 3.1)	0%
Lymphadenopathy		0%	0%	0%	0%
Lymphedema		0%	0%	0%	0%
Necrosis		0%	0.3% (0.0, 2.0)	0.4% (0.1, 3.1)	0%
Nipple complications (not related to sensation)		0%	0%	0%	0%
Nipple sensation changes		3.2% (2.3, 4.6)	1.4% (0.5, 3.7)	2.0% (0.8, 5.4)	0%
Other complications		0.6% (0.3, 1.3)	0.7% (0.2, 2.7)	1.1% (0.3, 4.4)	0%
Pneumothorax		0%	0%	0%	0%
Ptosis		1.8% (1.1, 2.8)	0.7% (0.2, 2.6)	2.0% (0.8, 5.3)	0%
Redness		0.3% (0.1, 0.9)	0.7% (0.2, 2.6)	3.0% (1.4, 6.6)	0%
Seroma/fluid accumulation		0.6% (0.3, 1.4)	1.2% (0.5, 3.3)	2.4% (1.0, 5.8)	1.3% (0.2, 8.7)
Skin rash		0%	0%	0.5% (0.1, 3.6)	0%
Skin sensation changes		0.4% (0.2, 1.1)	0.3% (0.0, 2.0)	0.9% (0.2, 3.5)	0%
Swelling		0.5% (0.2, 1.1)	0.7% (0.2, 2.6)	2.0% (0.7, 5.2)	0%
Upper pole fullness		0.1% (0.0, 0.9)	0%	0.6% (0.1, 3.9)	0%
Wrinkling/rippling		0.5% (0.2, 1.2)	2.4% (1.2, 4.8)	1.1% (0.3, 4.3)	1.5% (0.2, 9.8)

Table 12: K-M Risk Rates (95% CI) Though 3 Years

b. Main Reason for Reoperation

Table 13 shows the main reasons for reoperations, stratified by indication through 3 years. The rates are based on the total number of reoperations for that indication.

Reasons for Reoperation Through 3 Years*	Primary Augmentation N=149 reoperations	Revision-Augmentation N=84 reoperations	Primary Reconstruction N= 85 reoperations	Revision-Reconstruction N=38 reoperations
Suspected Rupture	0.0%	0.0%	1.2%**	0.0%
Infection	4.0%	3.6%	11.8%	2.6%
Capsular Contracture	22.1%	15.5%	8.2%	15.8%
Healing Related				
Extrusion	0.0%	1.2%	2.4%	0.0%
Necrosis	0.0%	0.0%	0.0%	0.0%
Hematoma/Seroma	11.4%	4.8%	3.5%	2.6%
Delayed Wound Healing	2.0%	6.0%	3.5%	0.0%
Irritation/Inflammation	0.0%	0.0%	0.0%	0.0%
Pain	0.7%	2.4%	0.0%	2.6%
Cosmetic				
Malposition	11.4%	13.1%	4.7%	10.5%
Upper Pole Fullness	0.7%	0.0%	0.0%	0.0%
Wrinkling	2.7%	9.5%	0.0%	2.6%
Palpability/Visibility	0.0%	1.2%	1.2%	0.0%
Asymmetry	3.4%	6.0%	18.8%	23.7%
Ptosis	12.1%	6.0%	5.9%	0.0%
Scarring	5.4%	3.6%	3.5%	0.0%
Nipple Related	1.3%	1.2%	1.2%	2.6%
Breast Cancer	0.7%	1.2%	0.0%	2.6%
Mass/Lump/Cyst	1.3%	0.0%	4.7%	5.3%
Skin related	0.0%	0.0%	1.2%	0.0%
Style/Size Change	19.5%	15.5%	24.7%	26.3%
Trauma	0.0%	0.0%	0.0%	2.6%
Other	0.0%	1.2%	0.0%	0.0%
Unknown	1.3%	8.3%	3.5%	0.0%

*Some reoperations were performed for multiple reasons; only the primary reason is provided in the table. In cases where multiple primary reasons for reoperation were given, the primary reason was determined using a hierarchy as defined by the listed order of reasons above.
** Confirmed non-ruptured via explant.

Table 13: Main Reason for Reoperation

c. Main Reason for Implant Removal

Table 14 shows the main reasons for implant removal, stratified by indication, through 3 years. The rates are based on the total number of explantations for that indication.

Reasons for Implant Removal Through 3 Years	Primary Augmentation N=103 explants	Revision Augmentation N=68 explants	Primary Reconstruction N=76 explants	Revision Reconstruction N= 30 explants
Suspected Rupture	0.0%	0.0%	1.3%*	0.0%
Infection	6.8%	4.4%	11.8%	3.3%
Capsular Contracture	13.6%	4.4%	3.9%	3.3%
Healing Related				
Extrusion	0.0%	0.0%	2.6%	0.0%
Necrosis	0.0%	0.0%	0.0%	0.0%
Hematoma/Seroma	1.9%	2.9%	1.3%	3.3%
Delayed Wound Healing	1.0%	0.0%	1.3%	0.0%
Irritation/Inflammation	0.0%	0.0%	0.0%	0.0%

Reasons for Implant Removal Through 3 Years	Primary Augmentation N=103 explants	Revision Augmentation N=68 explants	Primary Reconstruction N=76 explants	Revision Reconstruction N= 30 explants
Pain	0.0%	1.5%	0.0%	6.7%
Cosmetic				
Malposition	5.8%	4.4%	3.9%	10.0%
Upper Pole Fullness	0.0%	0.0%	0.0%	0.0%
Wrinkling	3.9%	11.8%	0.0%	3.3%
Palpability/Visibility	0.0%	0.0%	0.0%	0.0%
Asymmetry	4.9%	5.9%	18.4%	16.7%
Ptosis	1.9%	0.0%	0.0%	0.0%
Scarring	0.0%	0.0%	2.6%	0.0%
Nipple Related	0.0%	0.0%	0.0%	0.0%
Breast Cancer	1.0%	1.5%	0.0%	3.3%
Mass/Lump/Cyst	0.0%	0.0%	0.0%	0.0%
Skin Related	0.0%	0.0%	0.0%	0.0%
Style/Size Change	56.3%	39.7%	44.7%	43.3%
Trauma	0.0%	0.0%	0.0%	6.7%
Other	0.0%	4.4%	0.0%	0.0%
Unknown	2.9%	19.1%	7.9%	0.0%

*Confirmed non-ruptured via explant.

Table 14: Main Reason for Reoperation

d. Other Clinical Safety Outcomes

The following is a summary of the clinical findings from the study with regard to connective tissue disease (CTD), CTD signs and symptoms, cancer, reproductive complications, lactation complications, and suicide.

CTD Diagnoses

CTD diagnoses can include such diseases as fibromyalgia, systemic lupus erythematosus (SLE), discoid lupus, and scleroderma. Among primary augmentation patients, through Year 3, two patients (0.2%) report confirmed CTDs, which are one case of fibromyalgia and one case of rheumatoid arthritis. Among revision-augmentation patients, through Year 3, one patient (0.3%) reported a confirmed CTD, which is fibromyalgia.

Among primary reconstruction patients and revision-reconstruction patients, through Year 3, there are no confirmed CTD diagnoses.

CTD Signs and Symptoms

CTD signs and symptoms are collected every-other year (even years) throughout the study. Among the pooled primary augmentation and revision-augmentation patients, a statistically significant increase in the risk for CTD signs and symptoms was found in only 2 of the 13 CTD sign/symptom categories: pain and fibromyalgia, for which the statistical significance is driven by the prevalence of low back pain in both categories. Among the pooled reconstruction and revision-reconstruction patients, a significant

increase was found in only 1 of the 13 CTD signs/symptom categories: EENT, for which the statistical significance is driven by report of dry eyes. These increases in the two cohorts were not found to be related to simply getting older.

Cancer

For primary augmentation patients, through 3 years, there are two cases of breast cancer identified and no cases of fibrocystic breast disease. Diagnoses of any other (non-breast) cancers have been reported in 6 patients (less than 1%) in the augmentation cohort through 3 years.

For revision-augmentation patients, through 3 years, there is one case of breast cancer identified and no cases of fibrocystic breast disease. Diagnoses of any other (non-breast) cancers have been reported in 1 patient (0.3%) in the revision-augmentation cohort through 3 years.

For primary reconstruction patients, through 3 years, there are no cases of breast cancer or fibrocystic breast disease identified. Diagnoses of any other (non-breast) cancers have been reported in 7 patients (3%) in the primary reconstruction cohort through 3 years.

For revision-reconstruction patients, through 3 years, there are two cases of breast cancer identified and no cases of fibrocystic breast disease. Diagnoses of any other (non-breast) cancers have been reported in 1 patient (1.2%) in the revision-reconstruction cohort through 3 years.

Anaplastic Large Cell Lymphoma

There were no reports of anaplastic large cell lymphoma (ALCL) in any of the patient cohorts.

Lactation Complications

There are 150 primary augmentation patients reporting at least one postoperative live birth. Of these women, 88.7% report no difficulties with lactation. Twelve women (8%) reported postoperative lactation difficulties through 3 years. Of the 39 revision-augmentation patients experiencing at least one postoperative live birth, 2 (5%) reported postoperative lactation difficulties through 3 years. There are 16 primary reconstruction patients experiencing at least one postoperative live birth, and none (0%) reported lactation difficulties through 3 years. The one revision-reconstruction patient who experienced at least one postoperative live birth, reported no difficulties with lactation.

Reproduction Complications

Potential reproductive complications include miscarriage, preterm labor, and stillbirth.

Of the 1,115 patients in the primary augmentation cohort, 15 (1.3%) reported postoperative pregnancy difficulties through 3 years. Of the 362 patients in the revision-augmentation cohort, four (1.1%) reported postoperative pregnancy difficulties.

Of the 229 patients in the primary reconstruction cohort, 2 (0.9%) report postoperative difficulties through 3 years. Of the 82 patients in the revision-reconstruction cohort, none (0%) had postoperative difficulties.

Suicide

There are no reports of suicides in any of the patient cohorts.

e. Cumulative Risk for Occurrence of Each Complication at Each Follow-Up Assessment Point

The cumulative risk for first occurrence of each complication at each follow-up assessment point is presented in Table 15 below. The KM risk rates are presented by cohort for the 6 week, Year 1, Year 2, and Year 3 assessment points. The table begins with the cumulative risk of "Any Complication", followed by each complication in alphabetical order.

Complication	Study Cohort			
	Primary Augmentation	**Revision-Augmentation**	**Primary Reconstruction**	**Revision-Reconstruction**
Any Complication				
Week 6	3.3%	5.1%	9.7%	5.0%
Year 1	11.3%	15.7%	24.0%	21.9%
Year 2	16.0%	21.6%	38.4%	34.1%
Year 3	20.2%	26.3%	44.6%	43.2%
Asymmetry				
Week 6	0.2%	0.9%	1.8%	1.3%
Year 1	0.8%	1.4%	4.7%	2.6%
Year 2	1.0%	1.4%	6.9%	7.1%
Year 3	1.1%	1.8%	8.7%	7.1%
Breast Mass/Cyst/Lump				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0.5%	0%
Year 2	0.2%	0%	1.0%	3.1%
Year 3	0.3%	0%	1.0%	3.1%
Breast Pain				
Week 6	0.4%	0.6%	0.9%	0%
Year 1	0.6%	0.6%	0.9%	1.4%
Year 2	0.6%	0.6%	2.6%	1.4%
Year 3	0.8%	0.9%	2.6%	1.4%
Bruising				
Week 6	0.1%	0.3%	0.4%	0%
Year 1	0.1%	0.3%	0.4%	0%
Year 2	0.1%	0.3%	0.4%	0%
Year 3	0.1%	0.3%	0.4%	0%

Complication	Study Cohort			
	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
Capsular Contracture				
Week 6	0.4%	0.9%	1.8%	2.5%
Year 1	3.6%	2.4%	4.2%	5.1%
Year 2	4.8%	3.0%	6.4%	6.8%
Year 3	6.0%	5.2%	8.8%	6.8%
Capsule Calcification				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0%	0%
Year 3	0%	0%	0%	0%
Delayed Wound Healing				
Week 6	0.2%	0.6%	1.3%	0%
Year 1	0.2%	0.6%	1.3%	0%
Year 2	0.2%	0.6%	1.9%	0%
Year 3	0.2%	0.6%	1.9%	0%
Hematoma				
Week 6	0.7%	0.9%	0.4%	0%
Year 1	0.8%	0.9%	0.4%	0%
Year 2	0.8%	0.9%	0.4%	0%
Year 3	0.8%	0.9%	0.4%	0%
Hypertrophic/Abnormal Scarring				
Week 6	0.1%	0%	0%	0%
Year 1	0.3%	0%	1.0%	0%
Year 2	0.6%	0.7%	2.1%	3.1%
Year 3	0.6%	0.7%	2.7%	3.1%
Implant Extrusion				
Week 6	0%	0%	0.9%	0%
Year 1	0%	0.6%	0.9%	0%
Year 2	0%	0.6%	1.5%	0%
Year 3	0.1%	0.6%	1.5%	0%
Implant Malposition				
Week 6	0%	0.3%	0.5%	0%
Year 1	0.9%	1.8%	1.9%	3.9%
Year 2	1.0%	2.5%	3.0%	5.5%
Year 3	1.2%	3.2%	3.0%	5.5%
Implant Palpability				
Week 6	0%	0%	0.5%	0%
Year 1	0%	0.3%	0.5%	0%
Year 2	0%	0.3%	0.5%	0%
Year 3	0%	0.3%	0.5%	0%
Implant Visibility				
Week 6	0%	0%	0%	0%
Year 1	0.1%	0.6%	0.5%	0%
Year 2	0.1%	0.6%	1.0%	0%
Year 3	0.2%	0.6%	1.0%	0%
Infection				
Week 6	0.2%	0.3%	3.1%	1.2%
Year 1	0.5%	0.9%	4.0%	1.2%
Year 2	0.5%	1.2%	5.1%	1.2%
Year 3	0.7%	1.2%	5.1%	1.2%

Complication	Study Cohort			
	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
Irritation				
Week 6	0%	0%	0.4%	0%
Year 1	0%	0%	0.4%	0%
Year 2	0%	0%	0.4%	0%
Year 3	0%	0.4%	0.4%	0%
Lymphadenopathy				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0%	0%
Year 3	0%	0%	0%	0%
Lymphedema				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0%	0%
Year 3	0%	0%	0%	0%
Necrosis				
Week 6	0%	0.3%	0.4%	0%
Year 1	0%	0.3%	0.4%	0%
Year 2	0%	0.3%	0.4%	0%
Year 3	0%	0.3%	0.4%	0%
Nipple Complications: Not Sensation-Related				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0%	0%
Year 3	0%	0%	0%	0%
Nipple Sensation Changes				
Week 6	0.2%	0%	0.5%	0%
Year 1	0.7%	0%	0.9%	0%
Year 2	1.8%	1.0%	2.0%	0%
Year 3	3.2%	1.4%	2.0%	0%
Pneumothorax				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0%	0%
Year 3	0%	0%	0%	0%
Ptosis				
Week 6	0.1%	0%	0.5%	0%
Year 1	0.7%	0.3%	0.9%	0%
Year 2	1.3%	0.3%	2.0%	0%
Year 3	1.8%	0.7%	2.0%	0%
Redness				
Week 6	0.2%	0%	0.9%	0%
Year 1	0.3%	0.3%	1.9%	0%
Year 2	0.3%	0.3%	3.0%	0%
Year 3	0.3%	0.7%	3.0%	0%

Complication	Study Cohort			
	Primary Augmentation	Revision-Augmentation	Primary Reconstruction	Revision-Reconstruction
Seroma/Fluid Accumulation				
Week 6	0.1%	0.6%	1.3%	0%
Year 1	0.3%	0.9%	1.3%	1.3%
Year 2	0.5%	0.9%	2.4%	1.3%
Year 3	0.6%	1.2%	2.4%	1.3%
Skin Rash				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0.5%	0%
Year 2	0%	0%	0.5%	0%
Year 3	0%	0%	0.5%	0%
Skin Sensation Changes				
Week 6	0.1%	0.3%	0.9%	0%
Year 1	0.2%	0.3%	0.9%	0%
Year 2	0.2%	0.3%	0.9%	0%
Year 3	0.4%	0.3%	0.9%	0%
Swelling				
Week 6	0.5%	0%	0.9%	0%
Year 1	0.5%	0.3%	0.9%	0%
Year 2	0.5%	0.3%	2.0%	0%
Year 3	0.5%	0.7%	2.0%	0%
Upper Pole Fullness				
Week 6	0%	0%	0%	0%
Year 1	0%	0%	0%	0%
Year 2	0%	0%	0.6%	0%
Year 3	0.1%	0%	0.6%	0%
Wrinkling/Rippling				
Week 6	0.1%	0.3%	0%	0%
Year 1	0.3%	1.8%	0.5%	0%
Year 2	0.4%	2.4%	0.5%	1.5%
Year 3	0.5%	2.4%	1.1%	1.5%
Other Complications				
Week 6	0.3%	0%	0%	0%
Year 1	0.3%	0%	0%	0%
Year 2	0.5%	0.7%	1.1%	0%
Year 3	0.6%	0.7%	1.1%	0%

Table 15: K-M Risk Rates (95% CI) Though 3 Years for all time points

f. Risk Factor Analysis

A risk factor analysis was performed to determine whether there were any risk factors associated with the reported complications. The results of this analysis show that:

- No significant risk factors were associated with implant rupture.
- Device surface and placement were identified as risk factors for capsular contracture in augmentation patients. Both textured devices and submuscular device placement were found to be protective against capsular contracture; both

attributes were found to be associated with less capsular contracture than their counterparts (smooth-shelled devices and subglandular placement).

- In the reconstruction cohort, patient age at implantation was shown to be a risk factor for infection, reoperation and explantation. Older patients in this cohort have a higher risk of experiencing infection, reoperation, and explantation.
- In the revision-augmentation cohort, smooth shell surface was identified as a risk factor for reoperation; patients who received smooth-shelled implants were more likely to undergo a reoperation.

2. Effectiveness Results

The analysis of effectiveness was based on the 1,788 evaluable patients at the 3 year time point.

Effectiveness was assessed by bra cup-size change, circumferential chest size measurement, SF-36 subscale and aggregate scores (at baseline, 1 year post-surgery, and 2 years post-surgery), and scores on the Rosenberg Self-Esteem Scale and Body Esteem Scale (at baseline, 1 year post-surgery, and 2 years post-surgery).

Primary Augmentation Patients

For primary augmentation patients, 91% of patients increased their bra cup-size by at least one cup size (81% of patients increased their bra cup size by one to two cups, while 10% gained more than two cup sizes). Only 6% of patients achieved less than a one-cup size increase. The change is unknown for 3% of patients.

The majority of primary augmentation patients report favorable satisfaction results at Year 2 after their implant surgery. Over 90% of patients agreed that their breast implants make them feel more feminine (94%) and more attractive (92%). In addition, 85% of patients agreed that their breast implants made them feel better about themselves.

For all eight subscales and at all time points, including Baseline, the mean SF-36 QOL scores are significantly higher for the study population compared to the general female population, indicating that patients in the study who chose to undergo breast augmentation have a higher QOL than the average U.S. woman. Comparisons of Baseline QOL scores to scores at Year 2 show no clinically significant changes. There were a number of statistically significant decreases in the quality of life scales. However, effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant.

Primary augmentation patients reported high self-esteem scores at all time points, as measured by the Rosenberg Self-Esteem Scale. The mean total scores at Baseline and Year 2 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Mean scores on the Body Esteem Scale and subscales showed no clinically significant change from Baseline to Year 2 among women in the primary augmentation cohort. Scores are relatively high at baseline and remained high postoperatively.

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.

The majority of revision-augmentation patients in this study report favorable satisfaction results at Year 2 after their implant surgery. Most patients agreed that their breast implants make them feel more feminine (90%) and more attractive (89%). In addition, 82% of patients agreed that their breast implants made them feel better about themselves.

For all eight subscales and at all time points, including Baseline, the mean SF-36 QOL scores are significantly higher for the study population compared to the general female population, indicating that patients in the study who chose to undergo revision-augmentation have a higher QOL than the average U.S. woman. Comparisons of Baseline QOL scores to scores at Year 2 show no clinically significant changes. There were a number of statistically significant decreases in the quality of life scales. However, effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant.

Revision-augmentation patients reported high self-esteem scores at all time points, as measured by the Rosenberg Self-Esteem Scale. The mean total scores at Baseline and Year 2 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Mean scores on the Body Esteem Scale and subscales showed no clinically significant change from Baseline to Year 2. Scores are relatively high at baseline and remained high postoperatively.

Primary Reconstruction Patients

The majority of primary reconstruction patients in this study report favorable satisfaction results at Year 2 after their implant surgery. Most women agreed that their breast implants make them feel more feminine (79%) and more attractive (77%). In addition, the majority of women indicated that their breast implants made them feel better about themselves (72%).

For all eight subscales and at all time points, including Baseline, the mean SF-36 QOL scores were significantly higher for the study population compared to the general female population, indicating that patients in the study who chose to undergo breast augmentation have a higher QOL than the average U.S. woman. For primary reconstruction patients, comparison of baseline QOL scores to scores at Year 2 showed

no clinically significant changes. There were a number of statistically significant decreases in the quality of life scales. However, effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant.

For primary reconstruction patients, mean total scores on the Rosenberg Self-Esteem Scale at Baseline and Year 2 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Scores for the Body Esteem Scale and subscales showed no clinically significant change from Baseline to Year 2 among women in the primary reconstruction cohort. Scores were relatively high at baseline and remained high postoperatively.

Revision-Reconstruction Patients

The majority of revision-reconstruction patients in this study report favorable satisfaction results at Year 2 after their implant surgery. The study showed that most women felt their breast implants made them feel more feminine (76%) and feel more attractive (76%). In addition, the majority of women indicated that their breast implants made them feel better about themselves (73%).

For all eight subscales and at all time points, including Baseline, the mean SF-36 QOL scores were higher for the study population compared to the general female population. Comparisons of Baseline QOL scores to scores at Year 2 show no clinically significant changes in the second year as compared to baseline. There were a number of statistically significant decreases in the quality of life scales. However, effect sizes were small or very small and therefore the observed changes were judged not to be clinically relevant.

For revision- reconstruction patients, mean total scores on the Rosenberg Self-Esteem Scale at Baseline and Year 2 remained above 25. Scores between 15 and 25 are considered to be within normal range, with higher scores indicating more positive feelings.

Scores for the Body Esteem Scale and subscales showed no clinically significant change from Baseline to Year 2 among women in the revision-reconstruction cohort. Scores were relatively high at baseline and remained high postoperatively.

XI. RUPTURE RATE AND CONSEQUENCES OF RUPTURE

To assess the rupture rate and the consequences of rupture, FDA performed an extensive review of all available clinical and preclinical data. The clinical data included (a) the Sientra Clinical Study which includes a serial magnetic resonance imaging (MRI) cohort, (b) the *Long-Term Rupture Prevalence Study* from an different international study, and (c) and the published literature. The preclinical data related to rupture included the retrieval study and fatigue testing.

A. Clinical Study

Sientra's Study included rupture rate data from the MRI Cohort and the non-MRI Cohort. The study MRI Cohort is a randomized group of patients from the study population selected to undergo serial MRI screening at 3, 4, 6, 8, and 10 years to assess rates of silent rupture over time.

There were 383 patients successfully contacted to participate in the MRI Cohort and one patient was found to be deceased. Thirty-two patients were excluded due to claustrophobia or having had their study implants removed, leaving 351 patients available to undergo screening MRIs.

A total of 230 primary augmentation patients from the MRI Cohort underwent MRI screening; 98.5% of implants (97.4% of patients) have no evidence of rupture. Through Year 3, there are two confirmed (via explant surgery) and five unconfirmed implant ruptures occurring in six patients. The 3-year risk of rupture was 1.5% by implant and 2.5% by patient. In the case of the two confirmed ruptured implants via surgery, no extracapsular gel or gel migration was found.

A total of 74 revision-augmentation patients from the MRI Cohort underwent MRI screening and no evidence of rupture was found. In the non-MRI Cohort, there is one confirmed implant rupture occurring in one patient through Year 3. The 3-year risk of rupture among revision-augmentation patients in the Non-MRI Cohort is 0.2% by implant and 0.4% by patient. In the case of the confirmed ruptured, no extracapsular gel or gel migration was found. This patient did not undergo an MRI prior to explantation.

A total of 34 primary reconstruction patients from the MRI Cohort underwent MRI screening; 98.4% of implants (97.1% of MRI cohort patients) have no evidence of rupture. Through Year 3, there is one unconfirmed implant rupture. The 3-year risk of rupture is 1.4% by implant and 2.8% by patient. No ruptures are reported in the Non-MRI Cohort. One implant was suspected of being ruptured, but it was confirmed intact at explantation.

A total of 7 revision-reconstruction patients (12 implants) from the MRI Cohort underwent MRI screening and no evidence of rupture was found. Through Year 3, there are no confirmed or unconfirmed implant ruptures.

Table 16 below presents a summary of the MRIs conducted prior to explantation for suspected rupture. Among other things, the table includes the reason for undergoing the MRI and the rupture status of the device upon explantation. As seen in the table, two patients underwent MRI before explantation. Both patients had their implants removed due to suspected rupture. One patient's MRI results were consistent with the explant findings while the other patient's MRI results were not consistent with explant findings, indicating a false positive MRI reading.

Indication	MRI Cohort	Reason for MRI	Result of MRI	Reason for Implant Removal	Rupture Confirmation Status (via Implant)	Rupture Confirmation Status (via Retrieval Study)
Primary Augmentation	Yes	Screening MRI	Definitive intracapsular rupture bilaterally	Suspected rupture (asymptomatic)	Confirmed intracapsular rupture bilaterally	Confirmed bilateral rupture
Primary Reconstruction	No	Diagnostic MRI after injury to chest area	Suspected intracapsular rupture of left implant	Suspected rupture (symptomatic)	Confirmed non-ruptured	No, confirmed non-ruptured

Table 16: MRI Screenings Conducted Prior to Explanation

B. Long-Term Rupture Prevalence Study

The *Long-Term Rupture Prevalence Study*, a multicenter study conducted in four states in Brazil examined 274 implants in 140 women and assessed the rate of asymptomatic (or "silent") rupture in patients who received Silicone Gel Breast Implants between 1990 and 2000. Overall, the long-term prevalence of rupture in the study is 7.7% by implant and 12.1% by patient, with a median implantation age of 14.4 years. In comparison, those implants with no evidence of rupture suspected via MRI have a median duration of 10.2 years. These data support the low rate of rupture found in Sientra's Clinical Study and suggests that even over the long-term, over 14 years, Sientra's Silicone Gel Breast Implants have a relatively low rate of rupture.

C. Literature

A number of investigations have been conducted to examine the prevalence of rupture in patients with silicone gel breast implants of a variety of designs. The recent data suggest that for the most current implant designs, at a mean implantation time of approximately 10 years, the overall rupture rate for silicone gel-filled breast implants is less than 10% of implants. Heden et al. [7] examined 199 Inamed silicone breast implants (styles 40, 110, and 120) implanted in 106 women and reported that at a mean implantation time of 10.9 years, 183 (92%) of implants showed no evidence of rupture, 12 (6%) showed evidence of rupture, and four (2%) were indeterminate. Spear et al. [8] reported that at 6 years, the by-implant rupture rate for 715 female subjects in the Inamed clinical study of silicone gel-filled breast implants was 3.5%. Cunningham et al. [9] reported the results at 3 years for the Mentor clinical study on silicone Memory Gel breast implants. For the magnetic resonance imaging (MRI) cohort, the suspected rupture rates were 0.5% of patients for primary augmentation, 7.7% for revision-augmentation, 0.9% for primary reconstruction, and 0% for revision-reconstruction patients at 3 years.

Clinical studies and case reports provide some information on intracapsular rupture of breast implant patients. In most clinical studies in which the location of the gel was identified, intracapsular rupture was reported far more frequently than extracapsular rupture. Data from recently published studies suggest that of all ruptures, intracapsular ruptures typically

comprise more than 75% of the ruptures. Cunningham et al. [9] reported that for the MRI cohort of the Mentor core clinical study on silicone Memory Gel breast implants, there were eight ruptured/suspected ruptured implants in six patients (1.4% of patients) through 3 years. Of these eight implants, four showed intracapsular gel on MRI (50%). Heden et al. (2006) conducted a multicenter, cross-sectional study in which 106 women (199 implants) with at least one Inamed silicone gel-filled breast implant (styles 40, 110, and 120) underwent MRI examination. The imaging results showed clear evidence of rupture in 12 implants and indeterminate rupture in four implants (16 of 199, 8% of implants). Fifteen of the ruptures were classified as intracapsular (93.8% of ruptures).

Clinical studies provide information on extracapsular silicone gel in breast implant patients. In all cases, the devices were ruptured. Data from published studies of general populations of women with breast implants suggest that typically 10% of all ruptures are extracapsular. Cunningham et al. [9] reported the results of the Mentor clinical study on silicone MemoryGel breast implants. For the MRI cohort (420 patients), there were eight ruptured/suspected ruptured implants in six patients through 3 years. Of these eight implants, four showed extracapsular gel on MRI (two revision-augmentation patients and one primary reconstruction patient). Heden et al. [7] conducted a multicenter, cross- sectional study in which 106 women (199 implants) with at least one Inamed silicone gel- filled breast implant (styles 40, 110, and 120) underwent MRI examination. The imaging results showed clear evidence of rupture in 12 implants and indeterminate rupture in four implants. One of the indeterminate ruptures was classified as extracapsular (6.25% of all ruptures).

All of the evidence of migration of silicone gel from the breast implant site is available from case reports or series describing silicone gel found distant from a breast implant location. In virtually all cases, the implants are ruptured as a result of closed capsulotomies to treat capsular contracture, trauma, or compression mammography. Closed capsulotomy is no longer the treatment of choice for women with capsular contracture. The most commonly reported sites of silicone gel migration are the axilla, regional lymph nodes, and upper arm [10, 11].

Hölmich et al. [12] reviewed the available literature concerning breast implant rupture and connective tissue disease (CTD) and symptoms. They concluded that there is no association between implant rupture and well-defined connective tissue disease or undefined or atypical connective tissue disease. Hölmich et al. [13] conducted a clinical follow up of 238 of the 271 women from a prior study who completed a survey on disease and symptoms. They found that implant rupture was not associated with diseases or symptoms related to connective tissue diseases or other rheumatic conditions. Gaubitz et al. [14] examined 90 women with silicone breast implants using MRI and found that patients with ruptured implants were found to have complaints similar to patients with intact implants.

XII. SUMMARY OF OTHER CLINICAL INFORMATION

The scientific and medical literature was used to assess any association between silicone gel breast implants and the following health effects:

- cancer (both breast and non-breast)

- benign breast disease
- CTD diagnoses, signs and symptoms
- neurological disease, signs and symptoms
- interference of breast implants 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
- depression, anxiety, and suicide

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

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSION.S DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The most common complications through 3 years in the primary augmentation cohort were reoperation (12.6%) and Baker Grade III/ IV capsular contracture (6.0%). The most common complications for the revision-augmentation, primary reconstruction and revision-reconstruction cohorts were reoperation (20.3%, 34.9% and 42.5%, respectively) and implant removal with or without replacement (11.4%, 24.8% and 30.3%, respectively). The safety assessment of the study implants reveals clinically acceptable rates for complications associated with silicone breast implants, and, in general, demonstrate that the risk of complications associated with Sientra's breast implants is relatively low.

B. Effectiveness Conclusions

The effectiveness outcomes demonstrate that the majority of subjects report favorable satisfaction and Quality of Life results. In addition, the majority of patients who underwent a measurement of breast cup size change (augmentation cohort only), report an increase in bra cup-size by at least one cup size.

C. Overall Conclusions

Overall, the data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use. The 3-year clinical results demonstrate that the study implants are reasonably safe and effective for use in primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction of the breast.

XV. CDRH DECISION

CDRH issued an approval order on March 9, 2012. The final conditions of approval cited in the approval order are described below.

1. Post-Approval PMA Cohorts Study (PACS)

Per agreement reached on January 11, 2012 (e-mail), this study will consist of the continued follow-up of premarket cohorts. Study participants will be followed annually for 10 years in order to assess the long-term clinical performance of the device. The Post-Approval PMA Cohorts Study (PACS) will include a total of 1,788 subjects, which includes 1,683 subjects from the Core Study and 105 subjects from the reconstruction cohorts of the Continued Access Study, who were rolled into the Core Cohort for device approval. The PACS data are to be collected via annual physician follow-up evaluations and all patients in the study will have MRI at years 6, 8, and 10. All safety and effectiveness endpoints evaluated at premarket will continue to be studied long-term. The safety endpoints include local complications, implant rupture, connective tissue diseases (CTDs), CTD signs and symptoms, lactation complications, cancer and suicide. Descriptive statistics will be provided for all endpoints. In addition, the association between the studied endpoints and the approved device will be assessed as per agreement reached on January 11, 2012 (e-mail). Sientra sponsor is also required to conduct Device Explant Analyses for all devices retrieved from women enrolled in the PACS. They must report results of these explant analyses in the post-approval study Annual Report.

Sientra must also update their patient and physician labeling to reflect 5 and 10-year PACS study findings on the safety and effectiveness of the device, as soon as these data are available, as well as any other time point deemed necessary by FDA if significantly new information from this study becomes available. At 6 months, 1 year, and then on an annual basis, they must submit a PACS progress report to FDA that includes: (1) the follow-up status of study subjects; and (2) a summary of findings for all study endpoints.

2. Post-approval Continued Access Study (PACAS)

Per agreement reached on January 11, 2012 (e-mail), the Post-Approval Continued Access Study (PACAS) will consist of the continued follow-up, for 5-years post-implantation, of the 2,022 subjects in the primary augmentation cohort and 475 subjects in the revision augmentation cohort enrolled in the Continued Access Study. All safety and effectiveness endpoints evaluated premarket will continue to be studied through 5-years of follow-up. Descriptive statistics will be provided. Additional analyses will be performed as per

agreement reached January 11, 2012. Sientra is also required to conduct Device Explant Analyses for all devices retrieved from women enrolled in the PACAS. They must report results of these explant analyses in the post-approval study Annual Report.

Since the last patient of the PACAS was enrolled on July 20, 2007, the follow-up of all study participants should be completed in 2012. After the completion of 5-year follow-up for all PACAS subjects, they must submit a final report to FDA that includes: patient compliance and a summary of findings for all study endpoints.

3. US Post-Approval Study (US-PAS)

Per agreement reached on January 11, 2012 (e-mail), this study is a newly enrolled cohort study in the US. The purpose of this study is to evaluate the long-term clinical performance of Sientra Silicone Gel Breast Implants under general conditions of use in the postmarket environment. Enrollment of study subjects will begin within 90 days of PMA approval. The study will enroll 4,782 women receiving Sientra Silicone Gel Breast Implants and 300 women undergoing other aesthetic surgery as the comparison group. Study subjects will be followed annually for 10 years. Data will be collected on the following safety endpoints: connective tissue diseases (CTDs), rheumatologic and neurologic signs and symptoms, cancer (lung and breast, including the potential of breast implant interference with mammography and delay of breast cancer detection), suicide/attempted suicide, local complications (including infection, rupture, and rupture rate following mammography), reoperation and implant removal, reproductive complications in women who attempt to have children, lactation complications, and congenital deformities. The effectiveness will be assessed by Gel participants' responses to questions addressing their perceived quality of life and satisfaction with their breast implants.

Data are to be collected via annual patient questionnaires. There will also be physician evaluations at years 1, 5, and 9. Descriptive statistics will be provided for the studied endpoints. In addition, the association between the studied endpoints and the approved device will be assessed as per agreement reached on January 11, 2012. Sientra is also required to conduct Device Explant Analyses for all devices retrieved from women enrolled in the US-PAS. They must report results of these explant analyses in the post-approval study Annual Report.

Sientra must update their patient and physician labeling to reflect 5 and 10-year US-PAS study findings, as soon as these data are available, as well as any other time point deemed necessary by FDA if significantly new information from this study becomes available.

On a quarterly basis, Sientra must submit a report to FDA that includes: (1) the number enrolled by subjects receiving studied device versus enrolled in comparison group; (2) the number enrolled by indication (primary augmentation, revision-augmentation, primary reconstruction, revision-reconstruction) for subjects receiving studied device; (3) the number enrolled by race/ethnicity; (4) the enrollment rates versus the stated goals; (5) the reason why eligible patients were not enrolled into the study; and (6) the follow-up rates versus the stated goals. FDA will inform Sientra when quarterly reports are no longer necessary.

In addition, every 6 months for the first 2 years and then annually, thereafter, Sientra is to 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) the reasons why eligible patients were not enrolled into the study; (5) the follow-up rates versus the stated goals; and (6) a summary of findings for all study endpoints.

4. Post-Approval Case-Control Studies (PACCS)

Per case-control studies protocol included in P070004/A020 (submitted on October 4, 2011), the purpose of the Post-approval Case-control Studies (PACCS) is to evaluate the association between Sientra Silicone Gel Breast Implants and five rare disease outcomes (rare connective tissue diseases, neurological diseases, brain cancer, cervical/vulvar cancer and lymphoma). These studies will be conducted in Brazil and will enroll a total of 6,400 cases and 3,800 controls. For each of the five rare disease outcomes, 1,280 cases will be enrolled and compared to the controls on the history of the implantation of Sientra Silicone Gel Breast Implants.

On a quarterly basis, Sientra must submit a report to FDA that includes: (1) the number enrolled by cases and controls; (2) the enrollment rate versus the stated goal. FDA will inform Sientra when quarterly reports are no longer necessary. In addition, within 3 months of the completion of subject enrollment and data collection, Sientra must submit a final PACCS study report that includes the results and conclusions of the PACCS.

5. Focus Group Study

The purpose of the Focus Group Study is to evaluate 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, Sientra must submit a Final Report of the focus group study findings and suggested revision of patient and physician labeling based on those findings.

In addition to the studies listed above, Sientra must conduct non-PAS Device Explant Analyses for all Sientra Silicone Gel Breast Implants that are retrieved in the commercial setting outside the post-approval studies. On an annual basis, they must report the results of these Device Explant Analyses in the PMA Annual Reports.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVII. REFERENCES

1. *ASTM F703 - Standard Specification for Implantable Breast Prostheses.*
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