FDA Update on the Safety of Silicone Gel-Filled Breast Implants

June 2011

Center for Devices and Radiological Health
U.S. Food and Drug Administration

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I. Introduction

Breast implants are medical devices that are used to augment breast size or to reconstruct the breast following mastectomy or to correct a congenital abnormality. Breast implants consist of a silicone outer shell and a filler (most commonly silicone gel or saline). Approximately 5 to10 million women worldwide have breast implants.

According to the American Society of Plastic Surgeons National Clearinghouse of Plastic Surgery Procedural Statistics, there were 296,203 breast augmentation procedures and 93,083 breast reconstruction procedures performed in the United States in 2010. Approximately half the procedures used saline-filled implants and half used silicone gel-filled implants. Figure 1 shows a photograph of woman holding a breast implant.

Figure 1. Photograph of a woman holding a breast implant.

II. Purpose

The FDA approved two silicone gel-filled breast implants in November 2006. This report provides an update on the clinical information about these products. The report includes:

- Preliminary data from the post-approval studies that the FDA required manufacturers to conduct as conditions of approval;
- A summary and analysis of adverse events reported to FDA since approval; and
- A review and analysis of recent clinical publications about the safety and effectiveness of silicone gel-filled breast implants.

This document is not intended to provide a comprehensive clinical update about the safety of saline-filled breast implants. Updated labeling and other information about saline-filled breast implants can be found on the FDA website at www.fda.gov/breastimplants.

III. Overview

History of the Regulation of Silicone Gel-Filled Breast Implants

Silicone gel-filled breast implants were introduced to the U.S. in 1962. When the U.S. Congress passed the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, breast implants were considered moderate risk (Class II) devices and required to comply with general controls and performance standards. The FDA reviewed new breast implants through the 510(k) premarket notification process as it did other Class II products.

In the early 1980s, concerns arose about the safety of breast implants, in particular silicone gel-filled breast implants. FDA's new surveillance systems identified frequent local complications and adverse outcomes, and other published case reports described cancer and connective tissue disease in some women with breast implants. In response, the FDA reclassified breast implant into Class III, higher-risk products needing premarket approval (PMA), and called for manufacturers to provide data demonstrating the devices were safe and effective.

In 1992, the FDA determined that the manufacturers had not adequately addressed public concerns about certain complications, such as implant rupture and silicone leakage. Following the advice of an outside expert advisory panel, the FDA removed all silicone gel-filled breast implants from the market and required manufacturers to submit premarket approval applications that contained data on safety and effectiveness.

In order to meet a public health need, the FDA allowed manufacturers to provide silicone gel-filled implants for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Manufacturers enrolled women who received silicone gel-filled breast implants for these purposes in *Adjunct Studies* so that data could be collected about device performance and safety.

The FDA also called for more data on saline-filled breast implants, although it allowed them to remain on the market. During the next 14 years, with silicone gel-filled implants largely unavailable, many women opted for saline-filled breast implants.

In 1999, the Institute of Medicine (IOM) released a comprehensive report of the published literature and ongoing studies on breast implants, entitled *Safety of Silicone Breast Implants.*[1] The report made a clear distinction between local complications and systemic health concerns. It concluded that local complications were "the primary safety issue with silicone breast implants." These local complications, which included rupture, pain, capsular contracture, disfigurement, and serious infection, lead to medical interventions and repeat surgeries. Importantly, the IOM report concluded that there was no evidence that silicone breast implants caused systemic health effects such as cancer or autoimmune disease.

The FDA Breast Implant website, www.fda.gov/breastimplants contains a detailed Regulatory History of Breast Implants in the U.S.

U.S. Approved Silicone Gel-Filled Breast Implants

In November 2006, the FDA approved Allergan's* Natrelle Silicone Gel-Filled Breast Implants and Mentor's MemoryGel Silicone Gel-Filled Breast Implants. The FDA based its approvals on the manufacturers' clinical studies, called *Core Studies*, which followed hundreds of women with silicone gel-filled breast implants for 3 (Mentor) or 4 (Allergan) years. Despite frequent local complications and adverse outcomes, the FDA determined that the benefits and risks of breast implants were sufficiently well understood for women to make informed decisions about their use.

Data from each study are available in their respective PMA Summaries of Safety and Effectiveness. The FDA approved both devices for breast reconstruction for women of any age and breast augmentation for women at least age 22.

Postmarket Surveillance

When the FDA approved silicone gel-filled breast implants in the U.S. in 2006, it recognized that there were limited data on rare events and long-term outcomes. In order to better understand the long-term performance of these devices and to monitor for previously unrecognized adverse events, the FDA required the manufacturers to conduct post-approval studies, analyzed silicone gel-filled breast implant Medical Device Reports (MDR) submitted to FDA, performed periodic literature reviews, and evaluated correspondence from researchers, health care providers, patients, and concerned citizens.

Conditions of Approval

As conditions of approval, the FDA required each manufacturer of silicone gel-filled breast implants to conduct six post-approval studies to characterize the long-term performance and safety of the devices. The FDA believes that data from these long-term, post-approval studies will provide important information for women, their families and friends, and health care providers, and may lead to improvements in implant design and labeling.

Due to the length of the studies required by the FDA, they have not all been completed. Rather than waiting for all studies to be completed, FDA believes it is important to share currently available information so that women may make informed decisions about their health care.

The required post-approval studies for silicone gel-filled breast implants are as follows:

* Allergan was formally known as Inamed, which was formerly McGhan.

(1) *Core Post-Approval Studies (Core Studies)* – To assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications. These studies were designed to follow women for 10 years after initial implantation.

(2) *Large Post-Approval Studies (Large Studies)* – To assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients and following them for 10-years.

(3) *Device Failure Studies (Failure Studies)* – To further characterize the modes and causes of failure of explanted devices over a 10-year period.

(4) *Focus Group Studies* – To improve the format and content of the patient labeling.

(5) *Annual Physician Informed Decision Survey (Informed Decision Study)* – To monitor the process of how patient labeling is distributed to women considering silicone gel-filled breast implants.

(6) *Adjunct Studies* – To provide performance and safety information about silicone gel-filled breast implants provided to U.S. women from 1992-2006, prior to approval, when implants could only be used for reconstruction and replacement of existing implants.

IV. Detailed Summary of Post-Approval Studies for Silicone Gel-Filled Breast Implants

Key Points from Post-Approval Studies

- The FDA required each company to design and conduct six post-approval studies as conditions of approval.
- Key local complications and adverse outcomes observed include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection.
- The local complications observed in the silicone gel-filled breast implant post-approval studies are consistent with complications noted at the time of approval.
- The longer a woman has silicone gel-filled breast implants, the more likely she is to experience local complications or adverse outcomes. As many as 1 in 5 primary augmentation patients and 1 in 2 primary reconstruction patients require implant removal within 10 years of implantation.
- Limitations in the post-approval studies to date preclude the detection of very rare rates of complications. However, post-approval studies to date do not show evidence that silicone gel-filled breast implants cause connective tissue disease or reproductive problems.
- Differences in study design, clinical endpoints and definitions, and patient populations preclude direct comparisons of the post-approval study results for the two approved silicone gel-filled breast implants.
- Patient follow-up rates are lower than anticipated, limiting the ability to draw definitive conclusions and to detect rare complications.
- This represents an interim analysis of currently available data. Data collection is on-going.

NOTE: *This section contains detailed results from the post-approval studies of silicone gel-filled breast implants based on reports that the FDA received and validated as of May 31, 2011. Each manufacturer developed its own scientifically sound study design and statistical analyses. As a result, there are important differences between the two studies, including variations in number of study participants, patient enrollment criteria, clinical endpoints and definitions. These differences preclude direct comparisons of the two approved silicone gel-filled breast implants. In some cases, low patient follow-up rates may limit interpretation of the data.*

As conditions of approval, the FDA required Allergan and Mentor to conduct six post-approval studies, including: (1) *Core Studies*, (2) *Large Studies*, (3) *Device Failure Studies*, (4) *Focus Group Studies*, (5) *Annual Physician Informed Decision Studies*, and (6) *Adjunct Studies*.

For the *Large Study*, the FDA required each manufacturer to report interim study results twice each year for the first 2 years and annually thereafter. In addition, manufacturers provide quarterly updates on *Large Study* enrollment and follow-up. For all other studies, the manufacturers must submit annual reports to the FDA until study completion.

Both manufacturers have completed their *Focus Group Studies*. The other post-approval studies are ongoing. Both manufacturers have closed enrollment for their *Core Studies* and *Large Studies*. Follow-up in those studies continues but has been below target rates. Table 1 shows the enrollment and current follow-up status of each post-approval study.

Participants in the *Core Studies* and the *Large Studies* were enrolled in one of the following study cohorts:

- **Primary Augmentation** – women who received breast implants to increase the size of their breasts.
- **Primary Reconstruction** – women who received breast implants to replace breast tissue that was removed due to disease or trauma or that failed to develop properly.
- **Revision Augmentation** – women who received breast implants to correct or improve the results of primary breast augmentation surgeries.
- **Revision Reconstruction** – women who received breast implants to correct or improve the results of primary breast reconstruction surgeries.

Core Post-Approval Studies (*Core Studies)*

Purpose:
The purpose of the *Core Studies* was to gather data on longer-term safety and effectiveness of silicone gel-filled breast implants among participants enrolled in the studies conducted prior to approval, and to evaluate the effectiveness of magnetic resonance imaging (MRI) screening in detecting implant rupture.

Study Design:
The *Core Studies* followed participants enrolled in pre-approval studies of silicone gel-filled breast implants, and conducted clinical assessments of patients at six months, 1 year and annually thereafter for a total of 10 years.

Each study assigned participants to either an MRI group or a non-MRI group. Participants in the MRI group received MRIs on a specific schedule to screen for rupture. The timing of the MRI assessments and the methods of assigning participants to the MRI group differ by manufacturer. In addition, all participants (MRI group and non MRI group) received MRIs any time there were symptoms of a rupture.

The Allergan *Core Study* enrolled 715 patients and the Mentor *Core Study* enrolled 1,008 patients. Table 2 presents enrollment numbers for the *Core Studies* by indication, manufacturer, and MRI study group status.

Based on the 2010 annual reports, the preliminary follow-up rates at 10 years post-implant are 66 percent for Allergan, and at 8 years post-implant are 58 percent for Mentor (Table 1). Longer

term follow-up is available for the Allergan *Core Study* participants because the study began enrolling patients approximately 20 months before the Mentor *Core Study*.

Each study had some patients who were not available for follow-up because they had died or discontinued participation.

Final results should be available in 2012, after all patients have been followed for at least 10 years.

Results:

Local Complications and Adverse Outcomes

The most frequently observed complications and adverse outcomes in each *Core Study* include capsular contracture, reoperation, removal of the implant, and implant rupture. Other common complications cited in the Allergan study included asymmetry, scarring, and breast pain. Other common complications cited in the Mentor study included changes in nipple and breast sensation. Cumulative incidence rates of complications are displayed in Table 3 (Allergan) and Table 4 (Mentor).

Several observations can be made based on the available data. First, not surprisingly, the cumulative incidence rate of each complication increases over time.

Second, complication rates vary greatly depending on the type of surgery performed (primary vs. revision, augmentation vs. reconstruction). For many of the complications and adverse outcomes, rates are higher for patients undergoing revision augmentation and primary reconstruction than for primary augmentation. For example, the incidence of breast implant removal by 10 years post-implant for patients receiving Allergan silicone gel-filled breast implants is 32.4 percent for revision augmentation patients and 53.8 percent for primary reconstruction patients compared to 20.8 percent for primary augmentation patients. Similarly, for Mentor patients at 8 years post-implant, the incidence of breast implant removal is 21.1 percent for revision augmentation patients and 23.3 percent for primary reconstruction patients compared to 7.3 percent for primary augmentation. Detailed cumulative incidence rates of capsular contracture, reoperation, and implant removal are displayed in Table 5 and Table 6.

Third, the longer women had breast implants, the more likely they were to have them removed. In the *Core Studies*, Allergan reported a total of 293 implant removals over 10 years of follow-up, and Mentor reported a total of 195 implant removals over 8 years of follow-up. The most frequent reasons for implant removal for each study were capsular contracture, rupture, malposition, and wrinkling or ripping. Table 7 and Table 8 present data on the reasons for implant removal.

Finally, the most frequently reported reason for reoperation varied with type of surgery. A reoperation is defined as any additional surgical procedure performed on the breast and/or implant after initial breast implantation and includes minor surgical procedures such as breast biopsies.

In the *Core Studies*, Allergan reported 434 reoperations on 285 patients over 10 years, and

Mentor reported 385 reoperations on 276 patients over 8 years post-implant. The majority of silicone gel-filled breast implant patients in the *Core Studies* did not require reoperation.

For both manufacturers, capsular contracture and breast asymmetry were the most common reasons for reoperation in the primary augmentation and primary reconstruction groups, respectively. Other significant reasons for reoperation included the need for biopsy, breast cancer mass, implant malposition, breast sagging (ptosis), implant rupture, hematoma or seroma, scarring, and patient request for style or size change. Table 9 and Table 10 show details of the reasons for reoperations for each manufacturer.

Rupture Rates

In each *Core Study*, rupture rates varied by device and indication. The cumulative incidence of rupture rates among Allergan implants in the MRI group at 10 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	10.1 percent (7.4 to 13.7)
Revision augmentation	6.3 percent (2.8 to 13.7)
Primary reconstruction	27.2 percent (17.3 to 41.3)
Revision reconstruction	6.7 percent (0.2 to 31.9)

The cumulative incidence of rupture rates among Mentor implants at 8 years post-implantation (95 percent confidence intervals) were as follows:

Primary augmentation	13.6 percent (7.6 to 23.6)
Revision augmentation	15.5 percent (6.5 to 34.6)
Primary reconstruction	14.0 percent (7.6 to 25)
Revision reconstruction	21.3 percent (7.3 to 53.3)

In the Allergan *Core Study*, the majority of ruptures were accompanied by symptoms; depending on the cohort, up to 35 percent of ruptures may be silent.

Connective Tissue Diseases (CTD)

Among the Allergan *Core Study* participants, over 10 years of follow-up, there have been nine diagnoses of CTD. These include four cases of rheumatoid arthritis, three cases of fibromyalgia, one case of Raynaud's Syndrome, and one case of undifferentiated CTD.

Among the Mentor *Core Study* participants, over the 8- year period of follow-up, there have been 28 confirmed diagnoses of connective tissue, autoimmune, or rheumatic disease in 21 patients. These include seven reports of fibromyalgia, six cases of rheumatoid or inflammatory arthritis, three cases of chronic fatigue syndrome, three cases of thyroid-related disease, one case of systemic lupus erythematosis, and eight other miscellaneous and unspecified CTD cases.

Reproduction and Lactation Problems
In the *Core Study*, Allergan reported 45 post-implant reproduction problems in 44 patients over 10 years; most of the problems were spontaneous abortions, miscarriages or infertility. Most of the problems occurred in the primary augmentation and revision augmentation groups. In Allergan's primary reconstruction group, there was one report of a planned abortion to treat a medical problem and one report of no menses. There were no reports of post-implant reproduction problems among women who received the implants for revision reconstruction.

In Allergan's primary and revision augmentation groups, there were 30 post-implant problems with lactation reported in 24 patients, predominantly inadequate milk production. No post-implant lactation problems were reported among women who received the implants for reconstruction or revision reconstruction.

In the *Core Study*, Mentor reported 153 patients with pregnancies over 8 years. Twenty-three of these patients reported miscarriages, and one patient reported a stillborn delivery. Seventy patients reported attempting to breastfeed and of these, 13 reported lactation difficulties and nine reported an inadequate milk supply.

Breast Cancer
In the Allergan *Core Study*, 602 patients received silicone gel-filled breast implants for primary or revision augmentation. Of these, five were diagnosed with breast cancer through 10 years of post-implant follow-up.

In the Mentor *Core Study*, there were four new diagnoses of breast cancer among the 697 primary and revision augmentation patients through 8 years of follow-up.

Discussion:
The long-term follow-up of participants in the *Core Studies* demonstrates that a significant percentage of women who receive silicone gel-filled breast implants experience complications and adverse outcomes.

The most frequently observed complications and adverse outcomes include capsular contracture, reoperation, removal of the implant, and implant rupture. The cumulative incidence of these complications increases over time – the longer a woman has breast implants, the more likely she is to experience a complication.

These studies did not demonstrate an association of silicone gel-filled breast implants with CTD, reproductive or lactation problems, or breast cancer. However, it is important to note that these studies were not designed to estimate the incidence of rare disease outcomes, nor were they designed to compare silicone gel-filled breast implants to alternative therapies.

Large Post-Approval Studies (*Large Studies*)

Purpose:

The purpose of the *Large Studies* is to determine the incidence of complications and other adverse outcomes, including local complications, connective tissue disease, neurological disease, potential effects on offspring of women with breast implants, potential effects on reproduction and lactation, cancer, suicide, rupture, potential interference of breast implants with mammography, and patient compliance with recommendations for MRI follow-up.

The studies were designed to be large enough to address issues that the *Core Studies* were not powered to answer, as well as to provide a real-world assessment of some outcomes of silicone gel-filled breast implantation surgery.

Study Design:

Both Allergan and Mentor are in the midst of these 10-year, multi-center, prospective follow-up studies in women who received silicone gel-filled breast implants after FDA approval in 2006. Each study includes a control group of women who received saline-filled breast implants during the same time period.

In each of the *Large Studies*, participants are followed annually for 10 years. Data are collected using patient questionnaires (completed online, via mail, or telephone) and clinical follow-up visits (conducted three to four times during the course of the study).

Allergan designed its *Large Study* with 39,390 women with silicone gel-filled breast implants and a control group of 19,605 women with saline-filled breast implants. In October 2008, at Allergan's request, the FDA approved a reduction in the control group sample size to 15,240, based on FDA's calculation that this number of participants would be sufficient to meet the study objectives.

Allergan initiated patient enrollment in the *Large Study* in February 2007 and closed enrollment in March 2010, with a total of 41,342 silicone gel-filled breast implant recipients and 15,646 saline breast implant recipients. The results reported here are taken from Allergan's 2010 annual report. They include data for all participants with 2 years of follow-up.

Mentor's designed its *Large Study* with 41,900 women with silicone gel-filled breast implants and a control group of 1,000 women with saline-filled breast implants. Mentor initiated patient enrollment in the *Large Study* in February 2007, and closed enrollment in July 2009, with a total of 41,975 silicone gel-filled breast implant participants and 1,030 saline breast implant participants. The results reported here are taken from Mentor's 2010 annual report. They include data for all participants with 3 years of follow-up.

Among *Large Study* participants, 97 women enrolled in the Allergan study and 556 women enrolled in the Mentor study were under age 22, which did not meet the enrollment criteria. The tables and analyses of Allergan's data contained in this report include these patients. The tables and analyses of Mentor's data include only the 41,419 patients who met the original enrollment criteria. The FDA has asked Mentor to provide data and analyses on these younger women in future analyses.

Table 11 and Table 12 summarize the number of participants enrolled in Allergan's and Mentor's *Large Studies* by implant type and indication as reported in the 2010 study interim reports. In each company's *Large Study*, the majority of participants received implants for primary augmentation, with revision augmentation, primary reconstruction, and revision reconstruction occurring in decreasing frequency.

Results:

Baseline Social and Demographic Characteristics

Participants in Allergan's *Large Study* had a median age of 35, height of 5'5" and weight of 130 pounds. The majority of subjects were Caucasian (68.6 percent). Most attended or graduated from college (72.1 percent), were married (51.8 percent), and had professional occupations (45.2 percent). At baseline more than half of the participants (57 percent) had never smoked. More than two thirds of the current smokers (67.5 percent) reported smoking 10 or fewer cigarettes per day. The majority of subjects (63.3 percent) consumed no more than three alcoholic drinks per week, and 19.5 percent did not drink at all.

Among participants of known age in Mentor's *Large Study*, 78.2 percent of the silicone gel-filled breast implant participants and 49.8 percent of the saline breast implant participants were at least 30 years old. Among Mentor's participants in the primary augmentation group of known age, 70.4 percent of the silicone gel-filled breast implant recipients and 47.5 percent of the saline breast implant recipients were at least 30 years old. Silicone gel-filled breast implant participants had a median height of 5'5'' and median weight of 130 pounds. Saline breast implant participants had a median height of 5'3'' and median weight of 129 pounds.

Most participants in Mentor's *Large Study* attended or graduated from college (75.6 percent of silicone gel-filled breast implant recipients and 63.9 percent saline breast implant participants) and were married (59.5 percent silicone gel-filled breast implant recipients and 44.2 percent saline-filled breast implant recipients). For silicone gel-filled breast implant participants, 44.4 percent had ever smoked regularly and 70.7 percent were current alcohol drinkers. For saline breast implant participants, 38 percent had ever smoked regularly and 61.1 percent were current alcohol drinkers.

The FDA asked both manufacturers to closely monitor and report the racial/ethnic distribution of participants during the enrollment period to ensure participation that appropriately represented the demographics of the U.S.

The racial distribution of the Allergan *Large Study* participants at baseline was 71 percent Caucasian, 13 percent Hispanic, five percent Asian, three percent Black/African American and three percent other. There were six percent of participants for whom racial/ethnic information was unavailable.

In the Mentor *Large Study*, the racial/ethnic distribution of the Mentor MemoryGel silicone gel-filled implant recipients was 77.8 percent Caucasian/not of Hispanic origin, 9.9 percent Caucasian of Hispanic origin, 4.5 percent Asian, 2.2 percent Black not of Hispanic origin, 0.4 percent Black of Hispanic origin, 0.7 percent Native America/Alaska Native, 2.5 percent other,

and 2.1 percent unknown or not provided. Among the saline implant group in the Mentor study the race/ethnicity distribution was 56.5 percent Caucasian/not of Hispanic origin, 26.5 percent Caucasian of Hispanic origin, 7.7 percent Asian, 2.8 percent Black not of Hispanic origin, 1.2 percent Black of Hispanic origin, 0.9 percent Native America/Alaska Native, 4.6 percent other. Of note, for participants in the primary augmentation cohort of Mentor's study, for whom race/ethnicity was known, 76.7 percent of the MemoryGel participants and 54.7 percent of the saline participants were Caucasian, not of Hispanic origin.

Follow-Up

Follow-up rates reported to the FDA in the 2010 *Large Study* progress reports fell below targets. In addition, because not all women enrolled in the studies at the same time, follow-up duration varies. In some cases, these factors may limit interpretation of the data.

Allergan *Large Study* follow-up rates are 60.5 percent and 45.1 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively, 2 years after implantation. Follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	53 percent
Revision augmentation	55 percent
Primary reconstruction	75 percent
Revision reconstruction	69 percent

For the Mentor, *Large Study*, follow-up rates 3 years after implantation are 21.1 percent and 9.6 percent for silicone gel-filled breast implant participants and saline breast implant participants, respectively. The follow-up rates for silicone gel-filled breast implant participants by indication are:

Primary augmentation	20 percent
Revision augmentation	19 percent
Primary reconstruction	29 percent
Revision reconstruction	28 percent

Operative Techniques and Implant Characteristics

In the Allergan *Large Study*, 95.9 percent of participants received bilateral implants. Incision sites were most commonly inframammary (54 percent) and periareolar (22.8 percent). Most devices were placed either in a partial (58.9 percent) or complete (29.3 percent) submuscular position. The vast majority of implants had smooth surfaces (91.3 percent). In this study, the most commonly used implant size in both the silicone and saline cohorts was 300-399 cc (42.4 percent). The most common incision sizes were 4- 4.99 cm (32.5 percent) for silicone gel-filled

implants and 3-3.99 cm (43.2 percent) for saline implants, which reflect the fact that saline implants are filled after placement so the incision size can be smaller.

In the Mentor *Large Study*, 95.1 percent of silicone participants and 98.6 percent of saline control participants received bilateral implants. In the primary augmentation cohort, the inframammary surgical approach was used for 58.6 percent of the implants and 26.9 percent of the saline-filled implants. For silicone gel-filled and saline-filled participants, mastectomy scar was the most common surgical approach in the primary reconstruction cohort (72.8 percent and 57.9 percent respectively). The most common placement of the devices was submuscular for all cohorts in both treatment groups.

Local Complications and Adverse Outcomes
Allergan reports the 2-year cumulative incidence of local complications and other adverse outcomes as follows:

a. Reoperation. 6.5 percent for silicone gel-filled breast implant participants and 4.5 percent for saline breast implant participants.

b. Rupture. 0.5 percent for silicone gel-filled breast implant participants and 2.5 percent for saline breast implant participants (saline implant deflation).

c. Capsular Contracture (Grades III/IV). 5.0 percent for silicone gel-filled breast implant participants and 2.8 percent for saline breast implant participants.

d. Implant removal with or without replacement. 3.4 percent for silicone gel-filled breast implant participants and 2.4 percent for saline breast implant participants.

Mentor reports the 3-year cumulative incidence of local complications and other adverse outcomes for silicone gel-filled breast implant recipients as follows:

a. Reoperation. 10.8 percent for augmentation, 14.6 percent for revision-augmentation, 20.4 percent for reconstruction, 17.7 percent for revision-reconstruction.

b. Rupture. 0.2 percent for augmentation, 1.0 percent for revision-augmentation, 0.4 percent for reconstruction, 0.7 percent for revision-reconstruction.

c. Capsular Contracture (Grades III/IV). 5.3 percent for augmentation, 11.8 percent for revision-augmentation, 9.1 percent for reconstruction, 10.0 percent for revision-reconstruction.

d. Implant removal with or without replacement. 5.0 percent for augmentation, 7.7 percent for revision-augmentation, 13.5 percent for reconstruction, 11.7 percent for revision-reconstruction.

The *Large Studies* are collecting information on reasons for implant removal. In the Allergan study, the three most frequent reasons for device removal were desire to change size/style,

capsular contracture, and implant malposition. In the Mentor study, the three most frequent reasons for device removal were size change at patient request, infection, and asymmetry. Table 13 and Table 14 provide details of the reasons for device removals.

Rare Outcomes
In the Allergan *Large Study*, forty-three (0.6 percent) silicone gel-filled breast implant participants and 14 (0.4 percent) saline breast implant participants had new reports of CTD at 2 years follow-up. In the silicone gel-filled breast implant group, nine women reported fibromyalgia, four reported rheumatoid arthritis, nine reported fibromyalgia, three reported systemic lupus erythematosus, and 27 reported miscellaneous, undifferentiated, unspecified or "other" CTDs.

At 2 years follow-up, 80 silicone gel-filled breast implant subjects (1.2 percent) have reported a diagnosis of any cancer post-implantation. There were 18 silicone gel-filled breast implant participants with neurological disorders (0.3 percent) at year 2.

In the Mentor *Large Study*, the incidence rates per 10,000 person-years for CTD at 3 years follow-up were: 27.2 for rheumatoid arthritis (83 new cases), 70.9 for osteoarthritis (210 new cases), 3.9 for scleroderma (12 new cases), 4.2 for systemic lupus erythematosus (13 new cases), 5.9 for Sjögren's Syndrome (18 new cases), 22.4 for other connective tissue diseases (68 new cases), and 26.4 for fibromyalgia (80 new cases).

The incidence rates per 10,000 person-years for newly diagnosed cancer at 3 years follow-up were: 59.7 for all types of cancer (136 new cases), 13.6 for breast cancer (31 new cases), 0.9 for lung cancer (2 new cases), 0.0 for brain cancer, and 45.2 for other cancers (103 new cases). The incidence rate per 10,000 person-years for new neurological disease at 3-years was 36.0 for all types (111 new cases).

Discussion:
Reoperation, implant removal, rupture, capsular contracture, and other complications and adverse outcomes affect a significant proportion of women receiving silicone gel-filled breast implants. To date, the results of the *Large Studies* have not identified any previously unrecognized health concerns nor do they suggest a causal link between silicone gel-filled breast implants and CTD or breast cancer.

Data interpretation is limited due to low follow-up rates and the on-going nature of the study. The FDA has actively worked with the manufacturers to identify methods to improve the rate of study follow-up and to encourage patients and physicians to continue their participation in these studies.

Allergan conducted focus groups to better understand how patients may be motivated to complete follow-up visits and the annual questionnaire. Most respondents agreed that reminder e-mails, mailings, and telephone outreach would encourage them to continue participation.

Based on that feedback, Allergan launched a revised website for their *Large Study* that allows participants to complete the required questionnaire online. New options include personalized

pages, the ability to complete the questionnaire by phone, and the ability to update personal contact information online. In addition, Allergan issued a new direct-to-participant mailer. After these efforts, the annual number of complete questionnaires doubled.

To address their low *Large Study* follow-up rates, Mentor requested that the FDA write letters to patients and physicians. The FDA and Mentor sent more than 40,000 letters to study physicians and patients—these letters are available on the FDA Post-Approval Studies webpage. The letters encouraged ongoing patient participation and stressed the importance of continued follow up through study completion.

In response to these letters, Mentor and the FDA received significant feedback from study participants. Reasons cited by patients for failure to follow-up included geographical relocation, voluntary study discontinuation, and difficulty accessing the study website. The Mentor patient study webpage has since been modified at FDA's request.

Notably, *Large Study* follow-up rates vary by indication and appear consistent with findings identified in the *Core Studies.* Higher follow-up rates are observed among reconstruction participants, possibly because of their increased access to medical care for on-going monitoring of their underlying medical condition. It appears that once augmentation patients have received their implants and recovered from their surgery, they are less inclined to continue study participation than reconstruction patients.

Device Failure Studies (*Failure Studies*)

Purpose:

The purpose of these studies is to evaluate silicone gel-filled breast implants that have been retrieved and returned to Allergan and Mentor, and to document and catalog the failure modes in order to improve implant design and surgical techniques. Not all returned implants were removed because of local complications or rupture.

Each manufacturer was required to conduct studies of all retrieved devices returned to them until both the *Core Study* and the *Large Study* are completed. The data collection and analysis vary by manufacturer.

These studies are designed to: (1) further evaluate breast implant failures inadvertently caused during implantation, (2) characterize surgical instrument damage to breast implants, (3) evaluate and characterize failures that occur due to localized breast implant shell stress, and (4) determine if surgical factors (e.g., incision size) predispose to device rupture.

Allergan Results:

Since the beginning of its post-approval studies through June 30, 2009, 2,674 devices were returned to and analyzed by Allergan. Nine of these implants were excluded from the summary due to damage that occurred during shipping.

Allergan evaluated 2,665 devices in the laboratory with the following results:

- 87 (3.3 percent) devices could not be analyzed
- 1,429 (53.6 percent) devices were found to be "Intact and Functional," with no openings or other failure characteristics;
- 158 (5.9 percent) had "Gel Related Observations," with defects related to gel-related characteristics without loss of shell integrity.
- 91 (3.4 percent) had "Device Surface Observations," with defects related to the size or appearance of the device but not associated with an opening or deformation of the device.
- 900 (33.8 percent) had openings in the shell. Of the devices with openings:
    - 51 (1.9 percent) devices had fold flaws,
    - 26 devices (1 percent) had manufacturing defects,
    - 487 (18.3 percent) had surgical damage or surgical impact, and
    - 336 (12.6 percent) devices had openings for which the cause could not be identified.

Mentor Results:

Among patients participating in the Mentor *Large* post-approval study, 62 silicone gel-filled breast implants were retrieved; 35 (56.5 percent) were intact or without abnormality, and 27 (43.5 percent) had openings. Among the implants with openings, Mentor reported that 12 were damaged by sharp instruments and 15 had openings of unknown cause.

Among *Core Study* participants, 97 devices were explanted and returned to Mentor for evaluation from August 2000 to August 2009. Seventy-three of the 97 devices (75 percent) were returned intact and without abnormality. Of the 24 devices that ruptured, eight were damaged by sharp instruments, two had partial delamination in the shell or patch juncture, and 14 had a rent of unknown cause.

Discussion:

The most common cause of rupture reported in the device retrieval studies is damage to the implant during the implantation surgery. However, only a small proportion of breast implants are returned to the manufacturers for evaluation. This limits the ability to identify trends in failure modes.

Focus Group Study

Purpose:

The FDA required both manufacturers to complete *Focus Group Studies* to improve the format and content of the labeling. Both manufacturers completed their *Focus Group Studies* in 2007.

Allergan Focus Group Study:

Allergan's *Focus Study* had six focus groups, each of which had up to 10 participants, 18 years of age and older who had a breast implant or were considering breast implants. There were 29 augmentation breast implant participants and 23 reconstruction breast implant participants.

Based on its *Focus Group Study,* Allergan reorganized and modified its product labeling to include implant photos, graphs depicting change in cup size for augmentation, and additional information about patient satisfaction, quality of life, and long-term complications.

Mentor Focus Group Study:
There were four focus groups in Mentor's *Focus Group Study,* each of which had eight to 10 participants. Thirty-five adult women interested in silicone gel-filled breast implants for augmentation or reconstruction participated. Participants completed a self-administered survey designed to collect individual data and to measure their comprehension of information from Mentor's educational brochure. Respondents in both the augmentation and reconstruction groups agreed that the brochure was highly informative and comprehensive. Many respondents felt they learned new information as a result of reading the brochure. Based on the feedback from the focus groups, Mentor modified its brochure to more clearly outline differences between restoration, replacement, reconstruction, and revision and to provide information to help women weigh the risks and complications with the benefits of breast implants.

Annual Physician Informed Decision Survey (*Informed Decision Study*)

Purpose:
The FDA required both manufacturers to institute a formal informed decision process to ensure that: (1) a woman has obtained the patient information brochure with adequate time to read it prior to surgery, and (2) the surgeon has documented that the patient has an adequate understanding of the risks and follow-up recommendations associated with the device.

The FDA also required the manufacturers to provide physician training in the use of their informed decision process as part of physician training program for the implants. In addition, the FDA required each manufacturer to conduct a survey using a new random sample of 50 physicians each year to assess the patient informed consent process.

Results:
Based on the 2009 surveys for each manufacturer, physicians found the patients' brochures informative, useful, and effective in communicating breast implant risks and benefits. However, not all physicians use the brochure. For example, Allergan's survey showed that only 52 percent of physicians provide the brochure as part of the surgery consultation process.

Adjunct Studies

Purpose:
In 1992, when FDA removed all silicone gel-filled breast implants from the market, the FDA continued to permit companies to provide these devices for reconstruction after mastectomy, correction of congenital deformities, or replacement of existing implants. Women who received silicone gel-filled breast implants for these purposes were enrolled in *Adjunct Studies* so that data about device performance and safety could be collected. Participant enrollment began in 1992 for Mentor and 1997 for Allergan.

As a condition of approval of silicone gel-filled breast implants in 2006, both manufacturers were required to close enrollment of new patients into the *Adjunct Studies* but continue to follow study participants through their 5-year post-implant evaluations.

Allergan enrolled 83,968 women in its *Adjunct Studies*, including 44,799 who underwent primary reconstruction and 39,169 who underwent breast implant revision. The revision group included women who underwent both revision augmentation and revision reconstruction. Patients had a median age of 42 years (range, 14 to 98).

Mentor enrolled 136,609 women in its *Adjunct Studies*. Reconstruction surgery was performed in 57,828, revision reconstruction surgery in 18,491, and revision augmentation in 60,290 women.

Results:
The 5-year rates for the most common local complications and adverse outcomes observed in the Allergan *Adjunct Study* for patients undergoing primary reconstruction and revision, respectively, were capsular contracture (Baker III/IV) (16.3 percent, 22.6 percent), asymmetry (11.9 percent, 11.3 percent), implant palpability/visibility (7.7 percent, 12.2 percent), and wrinkling (6.2 percent, 9.4 percent).

For Mentor, the most common local complications and adverse outcomes in the primary reconstruction, revision reconstruction, and revision augmentation groups, respectively, were asymmetry (23.1 percent, 11.1 percent, 25.8 percent), wrinkling (13.4 percent, 14 percent, 17.4 percent), and explant (10.7 percent, 9.9 percent, 12.8 percent). Other reported additional procedures included nipple reconstruction, reconstruction revision/staged reconstruction, and capsulectomy. The most common reasons for removal were capsular contracture, infection, patient request for size and implant change, and leakage/rupture/deflation.

Discussion:
The *Adjunct Studies* provide qualitative information about the spectrum of adverse outcomes that occur in this patient population. However, data collection methodology and low follow-up rates (23 percent for Allergan and 16 percent for Mentor 5 years post-implant) limit data interpretation.

Post-Approval Study Conclusions

Overall, the post-approval studies conducted to meet the six conditions of approval demonstrate that the longer a woman has silicone gel-filled breast implants, the more likely she is to experience complications or adverse outcomes. The most common local complications and adverse outcomes associated with silicone gel-filled breast implants include capsular contracture, reoperation, and implant removal. Other local complications include implant rupture, wrinkling, asymmetry, scarring, pain and infection. Actual complication rates vary according to the reason for breast implantation.

These observations are consistent with complications and adverse outcomes previously known to

be associated with breast implants.

The post-approval studies to date do not show evidence that silicone gel-filled breast implants cause CTD, reproductive problems, or breast cancer. Low follow-up rates and other study limitations may limit interpretation of the data and preclude the detection of very rare complications.

Both manufacturers have encountered challenges in implementation of their study protocols, and follow-up rates are lower than expected. As follow-up has lagged, the FDA recognizes that these studies may not provide the data necessary to definitively answer questions about rare associations. The FDA has been working with manufacturers to address challenges related to enrollment and follow-up rates. See FDA Activities for more details.

For more information about breast implant post-approval studies, please visit the FDA Post-Approval Studies webpage.

V. Postmarket surveillance of adverse events reported on approved silicone gel-filled breast implants

Key Points from Postmarket Surveillance of Adverse Events

- The primary goals of FDA's postmarket medical device surveillance are to identify previously unrecognized adverse events and to help to detect patterns of actual or potential adverse events.
- Allergan and Mentor must submit adverse event reports on silicone gel-filled breast implants received after November 2006 through one of two reporting methods:
  - Medical Device Reports (MDR), or
  - Postmarket Spreadsheet Reports (PSR).
- Patients and healthcare providers can also submit adverse event reports directly to FDA through MedWatch, FDA's safety information and adverse event reporting program.
- Overall, the types of adverse events submitted to the FDA are consistent with results from premarket and post-approval studies. No unexpected outcomes or complications were reported through December 2010, except for rare reports of possible Anaplastic Large Cell Lymphoma (ALCL) associated with breast implants. For additional information on breast implants and ALCL see: Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants: Preliminary FDA Findings and Analyses.

Background:
The FDA collects and analyzes adverse event information from a variety of sources as part of its ongoing surveillance of silicone gel-filled breast implants.

Manufacturers and user facilities (such as hospitals and nursing homes) are required to submit device-related reportable events according the Medical Device Reporting (MDR) regulation (21 CFR Part 803). User facilities are required to report device-related deaths to FDA and device-related deaths and serious injuries to the manufacturer.

Allergan and Mentor must submit adverse event reports for patients who received silicone gel-filled breast implants through one of two reporting methods:

1) Medical Device Reports (MDR). Manufacturers must report all deaths and unusual, unique or uncommon adverse events to FDA as individual reports on the FDA Form 3500A within 30 days of becoming aware of the event, or

2) Postmarket Spreadsheet Reports (PSR). Manufacturers must report serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials in PSR reports. PSR reports are submitted quarterly, as authorized under 21

CFR Part 803.19(c), as an alternative to the requirement for submitting individual MDR reports on FDA Form 3500A.

Health care professionals, patients and other concerned individuals who do not have a mandatory reporting obligation, can submit reports voluntarily to the FDA through MedWatch, FDA's safety information and adverse event reporting program.

Individual reports submitted by breast implant manufacturers and user facilities are stored in FDA's Manufacturer and User Facility Device Experience (MAUDE) database, a repository for adverse event reports involving medical devices. Voluntary reports from health care professionals and patients are also stored in the MAUDE database. PSR reports are not included in the MAUDE database.

Postmarket Spreadsheet Reporting (PSR):
The FDA designed the PSR program specifically to monitor the postmarket performance of approved silicone gel-filled breast implants. The PSR program, an alternative to the requirement for submitting individual MDR reports, requires manufacturers to submit quarterly reports for serious injuries and malfunctions that are well-known or expected to occur based on data from the premarket clinical trials (e.g., rupture, capsular contracture).

The PSR program requires manufacturers to collect more specific and more detailed information about these well-known adverse events than would normally be submitted on an individual reporting form. The additional details include the patient's race/ethnicity, whether the patient is enrolled in the *Large Study*, the reason for implanting the device, whether a reoperation (with or without implant removal) was performed as a result of the adverse event, the reason for reoperation, the reason for implant removal, whether the removed implant was replaced and if so, with what type of implant, and the type of surgery performed. Collection of these data will help characterize the known breast implant-related problems and improve data analysis.

Reports from the MDR and PSR reporting systems are described in Tables 15 - 18. The data are grouped according to assigned patient problem codes and device problem codes. Patient and device problem codes are provided by the FDA for use by the manufacturer when submitting an adverse event report. (For more information about codes see Event Problem Codes).

Results of Postmarket Surveillance of Adverse Events:
Patient and Device Problems Submitted to the FDA as Individual MDRs
Between November 17, 2006 (date of FDA approval) and December 31, 2010, the FDA received 133 individual MDRs associated with Allergan and Mentor silicone gel-filled breast implants. Manufacturers submitted 24 of these reports, user facilities submitted 25 reports, and voluntary reports accounted for 84.

The types of events associated with these reports are two deaths, 84 serious injuries, 21 malfunctions, eight "data element is blank" and 18 "other" (a type of event used by the reporter when the adverse event is not considered a death, injury or malfunction report).

The two death reports referred to the same patient who was diagnosed with anaplastic large cell

lymphoma (ALCL). This patient's pathology report later confirmed that she had systemic ALCL, not ALCL localized to her breast implants. For more information about ALCL and breast implants see: Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants: Preliminary FDA Findings and Analyses.

The 133 reports contained a total of 530 patient problem codes and 239 device problem codes. Table 15 and Table16 list patient problems and device problems that occurred in more than 1 percent of the MDR reports.

Patient and Device Problems Submitted to the FDA through the Postmarket Spreadsheet Reporting (PSR) System
Between November 17, 2006 and December 31, 2010, the FDA received 16,681 reports through the PSR: 16,279 reports of injuries and 402 reports of implant malfunctions. A total of 26,511 patient problems were reported in 16,681 PSR reports.

The most frequent patient adverse events and outcomes reported were reoperations (noted by the code 'surgical procedure'), capsular contracture, pain, infection and breast lumps. The primary reasons for reoperations were rupture, capsular contracture, implant malposition/asymmetry, infection, wrinkling and hematoma. The primary reasons for implant removal were implant rupture, capsular contracture, malposition/asymmetry, infection, wrinkling and extrusion.

A total of 12,327 device problem codes were reported in 16,681 PSR reports. The most frequently reported device problems were device-patient incompatibility, rupture, implant malposition/asymmetry, and device defects that prevented the surgeon from implanting the device (includes codes for 'tears, rips, holes in device,' 'device material that prevented the device from being implanted,' 'design/structure problems,' and 'out of the box failures'). The term 'device-patient incompatibility' is a code used to indicate a biological reaction that the patient has to the implant.

Table 17 and Table 18 list patient problems and device problems that occurred in more than 1 percent of the PSR reports.

Discussion of Adverse Event Data:
There are strengths and limitations to the data collected through FDA's adverse event reporting systems. Strengths of the system include the ability to detect rare or unexpected device-related adverse events, the capacity to identify problems in the real world setting (unlike premarket trials) and collection of information about problems that occur over a long period of device use.

Because the number of patient and device problems reported to the FDA is subject to underreporting, MAUDE and PSR data are not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices.

Specifically, the MAUDE and PSR data are subject to a number of limitations, including:

- The number of events that are reported to the FDA is often much lower than the number of events that actually occur. Whether an event is reported may be influenced

by the severity of the adverse event, how unusual it is or whether there has been a lot of publicity or legal action involving the product.

- It is generally not possible to independently verify the reports received by the FDA. As a result, they may contain incomplete or inaccurate information. The FDA assumes that reports received are truthful.

- The size of the population exposed to the device (denominator) is often not known, so it is difficult to determine adverse event rates and put the number of adverse events in perspective to interpret the data.

- It is difficult to know whether or not the implant caused or contributed to the adverse event based solely on information provided in a report. Establishing a cause and effect relationship is especially difficult if the device is not examined or if the analysis was inadequate.

In summary, the results collected to date through the adverse event reporting system are consistent with the results obtained from the premarket and post-approval studies. With the exception of ALCL occurring in association with breast implants, no new complications or adverse outcomes associated with breast implantation have been identified.

VI. Review of the Literature on the Safety of Silicone Gel-Filled Breast Implants

Key Points from Literature Review

- This section reviews the epidemiologic literature published in peer-reviewed journals since 2005 on the clinical safety and effectiveness of silicone gel-filled breast implants. It focuses on outcomes that have not been addressed to date in post-approval studies.
- Most women report high levels of satisfaction with their body image and the shape, feel and size of their implants.
- Most infections develop in the immediate post-operative period, although infections can develop long after implant. Late infection may be underreported.
- The current body of literature does not support an association between CTD and silicone gel-filled breast implants, but most of the available studies have limitations.
- There is no evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility
- Current evidence does not support an association between mothers with breast implants and difficulty with breast feeding or adverse health events in their children.
- Women with breast implants may be more likely to be diagnosed with anaplastic large cell lymphoma (ALCL). See Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses.
- Although some studies show an increased risk of suicide in women with breast implants, this is likely due to selection bias. No study has demonstrated a causal relationship between breast implants and suicide.

Background:
At the time of their approval in November 2006, silicone gel-filled breast implants were associated with several well-characterized complications and adverse outcomes, including rupture, reoperation, and capsular contracture. Data concerning these results are presented in the Post-Approval Study (Section V) and Post-Market Surveillance of Adverse Event (Section VI) sections of this report and are not discussed here.

When the FDA approved Allergan and Mentor's silicone gel-filled breast implants in 2006, there were reports of other potential adverse events, but they were infrequent and not fully understood. These included implant-related infections, CTD, cancer, reproductive outcomes, and suicide. In addition, there were limited data on patient satisfaction. These results are discussed in this section.

This section summarizes medical and scientific English literature published primarily from January 1, 2005 through December 31, 2010. The literature search included reviews and meta-analyses of human studies, as well as selected original papers. If significant publications concerning a particular adverse event of interest had not been published during the relevant time period, manuscripts from earlier time periods were evaluated.

Patient Satisfaction and Quality of Life:

Satisfaction of patient expectations remains an important measure of the effectiveness of cosmetic surgery. Patients undergoing breast augmentation surgery have reported high rates of satisfaction with the shape, feel, and size of their silicone gel-filled breast implants.[2-8]

Studies show that many women undergo breast augmentation surgery to improve their self-esteem and self-image.[2, 5] More than 90 percent of women with silicone gel-filled breast implants are satisfied that their primary expectations have been met. Body image improves in the majority of women who receive silicone gel-filled breast implants, and this satisfaction lasts for at least two years post-implant.

Post-operative complications such as capsular contracture decrease satisfaction with the procedure, particularly if those complications are visible to other people.[2]

Infections:

Estimates from scientific and medical literature on the risk of infection following silicone gel-filled breast implantation are derived mainly from prospective studies in Scandinavian countries.[9, 10] Wound infections occur in less than 5 percent of breast implant study participants. Along with hematoma, infections are the most common short-term local complication. Infections generally occur in the immediate period following surgery.[9] Systemic infections are not typical although toxic shock syndrome has been rarely reported.[11]

Acute infections associated with breast implants are generally linked to skin pathogens (i.e., group A streptococci, Staphylococcus epidermidis, or Staphylococcus aureus), while long-term infections are often caused by aerobic gram-negative bacilli. Chronic "culture-negative" infections after breast implant procedures are sometimes due to atypical mycobacteria. Although two-thirds of infections develop within the acute post-operative period, some infections may develop years or even decades after surgery. The reported rate of systemic and late infections is approximately 1 percent or less, although it is likely that late infections are under-reported.[12, 13]

Subclinical infection may predispose to long-term complication that follows breast implantation, i.e., capsular contraction that involves the formation and contraction of a collagenous sheath around the implant, thus forming hard, spherical masses in the breasts.

While systemic postoperative wound infections are rare, the effects can be devastating. Among the Mycobacteria, Mycobacterium fortuitum complex represent the opportunistic pathogens that account for 60 to 80 percent of postsurgical wound infections caused by rapidly growing mycobacteria, particularly after breast surgery (with or without prosthetic implants).[14-16] Complications include long term infection occurring months after implantation. Drainage or

implant removal is usually required to ensure bacterial eradication.[17]

Connective Tissue Diseases/Rheumatic Conditions:

Connective tissue diseases (CTDs) include a spectrum of conditions such as fibromyalgia, scleroderma, Sjögren's Syndrome, and systemic lupus erythematosus. A number of studies evaluated the possibility of a relationship between silicone gel-filled breast implants and connective tissues diseases.[18-37]

Estimate of CTD differ. For example, the incidence of fibromyalgia is approximately 1,128 women per 100,000 women in the general population according to one study.[38] Comparatively, the incidence of scleroderma in a general population is much lower, occurring in approximately 3 patients per 100,000 per year.[39]

Because of the incidence and prevalence[40] of CTDs are quite low,[38, 39] a very large study of sufficient duration would be required to determine a causal relationship between silicone gel-filled breast implants and CTD.

Most studies have not found an association between connective tissue diseases as a group and silicone gel-filled breast implants. The FDA collaborated on one study in 2001 that found a positive association between extracapsular silicone gel-filled breast implants and fibromyalgia, but significant study design and patient selection weaknesses undermine the study's conclusions.[41]

Most studies that have examined specific connective tissue diseases like fibromyalgia, scleroderma and systemic lupus erythematosus have failed to identify an association, although the studies have recognized limitations, such as lack of very long-term duration of follow-up.[25, 33, 37]

Overall, the current body of evidence does not support an association between silicone gel-filled breast implants and CTD.

Cancer:

Women who receive silicone gel-filled breast implants for augmentation do not appear to be at increased risk of developing breast cancer.[42, 43] In fact, studies suggest they may be at average or even lower risk – with some estimating a risk reduction of 10 to 50 percent.[44]

Survival rates for women with breast cancer who receive silicone gel-filled breast implants as part of breast reconstruction appear to be unaffected by the presence of an implant.[44]

Some reports have observed an increase in cancer risk for patients with cosmetic breast implants (not specifically silicone gel-filled breast implants), including brain, cervical, vulvar, lung, and non-melanoma skin cancer.[45] However, these observations appear unrelated to the effects of the implants themselves.[10, 46] Post-approval studies have not identified an increased cancer risk among silicone gel-filled breast implant recipients.

One possible exception is the rare development of Anaplastic Large Cell Lymphoma (ALCL) in

women with breast implants. Reports in the scientific community have suggested a possible association between ALK-negative ALCL and silicone gel-filled and saline-filled breast implants. In a thorough review of scientific literature published from January 1997 through May 2010, the FDA identified 34 unique cases of ALCL in women with breast implants throughout the world. The FDA's adverse event reporting systems also contain 17 reports of ALCL in women with breast implants. Additional cases have been identified through the FDA's contact with other regulatory authorities, scientific experts, and breast implant manufacturers. In total, the FDA is aware of approximately 60 case reports of ALCL in women with breast implants worldwide. For additional information, see Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses.

Other than ALCL, the available epidemiologic evidence does not support a clinical association of silicone gel-filled breast implants with an increased cancer risk in humans. Results from several recent published large scale cohort studies with long-term follow-up provide no evidence of an association between breast implants and cancer.[42, 43, 47]

Screening for Breast Cancer:
Screening mammograms are X-ray images of the breast used to look for changes in the breast tissue that are too small to cause noticeable symptoms; in some cases these represent breast cancers.[48] Breast implants may make it difficult to see breast tissue on standard mammograms; additional X-ray images, called implant displacement views, can be obtained at the time of a mammogram and should be used to examine the breast tissue more completely in breast implant patients.[49]

The National Cancer Institute advises women with breast implants to receive screening mammography, at experienced centers, at intervals based on their age and risk factors. Women should be sure to notify the mammography facility and the technologist conducting the exam that they have breast implants.

The National Cancer Institute recommendations for breast cancer screening in women with breast implants can be found at http://www.cancer.gov/cancertopics/factsheet/Detection/mammograms.

Screening for Rupture:
When a silicone gel-filled implant ruptures, the gel may remain in the shell or in the scar tissue that forms around the implant (intracapsular rupture). In some cases, the silicone migrates outside of scar capsule (extracapsular rupture). It may be difficult or impossible to remove silicone gel that has migrated out of the capsule to other parts of the body.

Different diagnostic tests can be used to detect intracapsular and extracapsular breast implant rupture, including magnetic resonance imaging (MRI), mammography, ultrasound, and computed tomography (CT).

MRI can be used to detect both intracapsular and extracapsular ruptures. In the older models of silicone gel-filled breast implants, MRI can detect more than 90 percent of ruptures.[50]

A recent meta-analysis on the diagnostic accuracy of MRI for detecting silicone gel-filled breast implant ruptures reported lower accuracy in detecting ruptures in asymptomatic patients than in symptomatic patients.[51]

One of the post-approval studies required by the FDA looks at the accuracy of MRI in detecting rupture.

The FDA approved labeling for silicone gel-filled implants currently recommends that women get their first breast MRI 3 years after they receive the implants and every 2 years thereafter to detect silent ruptures.

MRIs are not an option, however, for women who have MRI incompatible pacemakers, aneurysm clips, or other implanted metallic foreign bodies, or whose physical size and weight precludes them from having an MRI.[50]

Once implants are removed, there is no medical need for routine screening MRI.

Mammograms can detect extracapsular silicone when an implant ruptures, but they do not detect intracapsular ruptures. In older models of silicone gel-filled breast implants, only 10 to 22 percent of ruptures are extracapsular, so mammograms will miss most ruptures.[50] If extracapsular silicone is detected by mammography, before making a presumptive diagnosis of implant rupture, the physician should take a careful clinical medical history from the patient to rule out the possibility that the silicone remains from a prior rupture or silicone injection (and thereby unrelated to the current silicone gel-filled breast implant).

The relative value of ultrasound alone to detect intracapsular ruptures is controversial because its accuracy depends on the skill of the ultrasound technologist, the type of equipment used, and the experience of the interpreting physician.[50] Ultrasound is limited in its ability to detect ruptures in the back wall of the implant and in the breast tissue behind it. Extracapsular silicone has a distinctive appearance on ultrasound and should be recognized if imaged. As with mammography, extracapsular silicone detected on ultrasound may be due to a previous implant rupture or silicone injection. Therefore, a thorough clinical history is important to make an accurate diagnosis.

CT scans can detect intracapsular silicone gel-filled breast implant rupture, but they are limited in their ability to detect extracapsular ruptures. This imaging technique is a useful alternative for women who are unable to have MRIs. However, a disadvantage of CT is that it exposes patients to ionizing radiation.[50]

Effects on Reproductive Outcomes:
There is no significant evidence that suggests untoward effects of silicone gel-filled breast implants on pregnancy or fertility.

The bulk of the published literature in the field of maternal and child health to date does not suggest a causal relationship between silicone gel-filled breast implants and adverse health outcomes in children born to women with implants.[10, 52] In addition, silicone gel-filled breast

implants do not appear to be associated with breastfeeding difficulties.[53, 54]

Suicide:
Retrospective studies consistently suggest an increased rate of suicide in patients undergoing breast implants compared to the general population. However, it is likely that this reflects underlying factors including socioeconomic status and self-esteem. There is no evidence that breast implants cause the observed increase in suicide risk.[55-58]

VII. Summary of Key Findings

1. Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use.

2. The longer a woman has breast implants, the more likely she is to experience local complications or adverse outcomes. Women with breast implants will need to monitor their breasts for local complications for the rest of their lives.

3. The most frequent complications and adverse outcomes experienced by breast implant patients include capsular contracture, reoperation, and implant removal (with or without replacement). Other frequent complications include implant rupture, wrinkling, asymmetry, scarring, pain, and infection, among others. These observations are consistent with the local complications and adverse outcomes that were known at the time of approval.

4. Women with breast implants may have a very small but increased likelihood of being diagnosed with anaplastic large cell lymphoma.

5. In the post-approval *Core Studies*, between 20 to 40 percent of augmentation patients and 40 to 70 percent of reconstruction patients had reoperations during the first 8 to 10 years after they received their implants. Although routine replacement is not necessary, many women will need additional surgery to modify, remove, or replace their implants.

6. There is no apparent association between silicone gel-filled breast implants and connective tissue disease, breast cancer, or reproductive problems. Associations that are very rare or that take many years to manifest may not be detected using currently available data.

7. MRI continues to be the most effective method of detecting silent (asymptomatic) rupture of silicone gel-filled breast implants.

8. Interpretation of the data from the silicone gel-filled breast implant post-approval studies may be limited by low follow-up rates.

VIII. Recommendations for Patients Who Have or Who Are Considering Breast Implants

- Be aware that breast implants are associated with significant local complications, and the longer the devices remain implanted, the more likely you are to experience a complication. Local complications and adverse outcomes include capsular contracture, reoperation, removal, and implant rupture. Many women also experience breast pain, wrinkling, asymmetry, scarring, and infection.

- Continue to receive routine follow-up with your physician. This includes having periodic MRI exams to detect "silent rupture" of the implant.

- Notify your health care provider if you develop any unusual signs or symptoms including pain, asymmetry, hardness or swelling.

- Recognize that breast implants are not lifetime devices. The longer you have your implants, the more likely it will be for you to have them removed.

- If you have enrolled in an Allergan or Mentor post-approval study, continue to participate. These studies are the best way to collect information about the long-term rates of complications.

- Continue routine screening mammography for breast cancer at intervals recommended by your health care provider based on your age and risk factors.

IX. Recommendations for Health Care Providers

- Provide women with copies of patient brochures and informed consent so that they have access to the critical information needed to make informed decisions about receiving and caring for breast implants. Labeling for Approved Breast Implants for patients and for physicians is available on FDA's breast implant website.

- Maintain medical vigilance through follow-up and post-approval studies so that the long-term effects of silicone gel-filled breast implants can be better understood. Your contributions provide data that are used to evaluate how new surgical techniques, patient characteristics, and implant characteristics influence the cosmetic and health outcomes of patients undergoing breast implantation.

- Screen for silent rupture using MRI. Women with silicone gel-filled breast implants should undergo MRI screening for silent implant ruptures at 3 years post-implantation, and every 2 years thereafter.

- Report breast implant associated adverse events and deaths to FDA via MedWatch.

X. FDA Activities

The FDA activities surrounding silicone gel-filled breast implants focus on three key goals:

- Fostering the collection of data about implant performance;
- Improving the follow-up rates in current and future post-approval studies; and
- Communicating new safety information when it becomes available so that women can make informed decisions about their healthcare.

To accomplish these goals, the FDA:

- Closely monitors the status and conduct of the on-going required post-approval studies so that data is collected, validated scientifically and disseminated widely;

- Actively encourages and facilitates adverse event reporting by the manufacturers, patients, healthcare providers, and health care facilities;

- Is collaborating with the American Society of Plastic Surgeons (ASPS) and other experts in the clinical and scientific community to develop a registry of women with breast implants and anaplastic large cell lymphoma (ALCL) to better understand the nature and possible factors contributing to their association;

- Will hold a meeting of its Medical Device Advisory Committee in the summer of 2011 to seek input on issues related to postmarket surveillance of silicone breast implants including study design, patient enrollment and follow-up, and data analysis;

- Released, in June 2011, a newly updated breast implant website (www.fda.gov/breastimplants). Key sections of this website describe the risks of breast implants, the questions women should ask their doctors before getting breast implants, and what women should expect during the surgical procedure and recovery.

- Developed a new Breast Implants Complications Booklet for patients. The booklet includes the latest information from the post-approval studies. It is available on the FDA website.

- Requires breast implant manufacturers to update their labeling each time the data is reanalyzed. The most current Labeling for Approved Breast Implants is available on the FDA website.

XI. Conclusion

Based on the totality of the evidence, the FDA believes that silicone gel-filled breast implants have a reasonable assurance of safety and effectiveness when used as labeled. Despite frequent local complications and adverse outcomes, the benefits and risks of breast implants are sufficiently well understood for women to make informed decisions about their use. Manufacturers and physicians should continue to provide balanced and up-to-date information to women considering breast implants to help inform their decisions.

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XIII. Glossary of Terms

Adverse Event Report: A report submitted to the FDA describing an undesired outcome for which a device association is known or suspected. Also known as a Medical Device Report (MDR).

Adjunct Studies: Specific to silicone gel-filled breast implants, these studies were originally designed by FDA to address the public health need for reconstruction and revision patients. By participating in these studies women and surgeons gained access to the silicone gel-filled breast implants not on the open market.

ALCL: Anaplastic Large Cell Lymphoma, a rare type of T-cell non-Hodgkin's lymphoma. ALCL is a rare type of non-Hodgkin's lymphoma. ALCL is not cancer of the breast tissue. Lymphoma is a cancer of the lymphatic cells of the immune system.

Asymmetry: Lack of proportion of shape, size, and/or position between the two breasts.

Augmentation: A surgical procedure to increase breast size. For this document, it refers to placement of a breast implant. The first time a breast implant is placed to increase breast size, it is called primary augmentation. All subsequent times the implant is replaced, it is called revision augmentation.

Capsular Contracture: A tightening of the fibrous capsule surrounding a breast implant, resulting in firmness or hardening of the breast. One of the most common complications of breast implant surgery.

Capsulectomy: The surgical removal of capsular contracture around the breast implant

Capsulorraphy: A surgical procedure to revise the shape and size of the pocket in which the breast implant lies.

Class III device: FDA uses a risk based model to assign devices into one of three classifications: Class I, II, or III. A Class III designation represents the highest risk profile. A Class III device requires premarket approval and a scientific review to ensure the device's safety and effectiveness, in addition to the general controls for lower risk devices.

Cohort: a group of study participants who share similar conditions, characteristics or demographics

Condition of Approval: Postmarket obligation defined by FDA that the manufacturer must comply with as part of the terms for receiving authorization to market a specific device.

Connective Tissue Disease (CTD): any disease that targets the connective tissues of the body; they may be heritable (such as fibromyalgia), autoimmune (such as rheumatoid arthritis) or other (such as scurvy).

Core Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies is to assess long-term clinical performance of breast implants in women that enrolled in studies to support premarket approval applications.

Epidemiologic Study: A statistical study on a human population that attempts to link health outcomes with a specific cause.

Extracapsular: Occurring outside the fibrous scar capsule surrounding the breast implant.

Federal Food, Drug, and Cosmetic Act: The law which gives FDA its regulatory authority.

Follow-up rates: the indication of how often the manufacturer maintains contact with the patient after the initial breast implant surgery in the collection of post-implant study data. The follow-up rate reflects the manufactures success in data collection.

Focus Group Studies: A form of quality research in which participants are gathered together and are asked about their perceptions, opinions, beliefs and attitudes towards a specific issue or item. Questions are asked in an interactive group setting where participants are free to talk with other group members.

Iatrogenic Injury/Damage: Injury or damage an implant resulting from a surgical procedure.

Institute of Medicine (IOM): The Institute of Medicine is a US not for profit governmental organization. Its purpose is to provide national advice on issues relating to biomedical science, medicine, and health, and its mission to serve as adviser to the nation to improve health. It works outside the framework of the U.S. federal government to provide independent guidance and analysis.

Intracapsular: Occurring inside the fibrous scar capsule surrounding the breast implant.

Lactation: the act of producing milk from the mammary glands in the breast.

Large Studies (specific to breast implants): Clinical studies on silicone gel-filled breast implants required of Mentor and Allergan after the FDA approved their devices in 2006. The purpose of these studies was to assess long-term outcomes and identify rare adverse events by enrolling more than 40,000 silicone gel-filled breast implant patients, following them for 10-years, and comparing them to control groups of saline-filled breast implant patients.

Mammography: An x-ray of the breast tissues

Meta-analysis: A combined evaluation of multiple similar studies

MRI (Magnetic Resonance Imaging): a diagnostic testing process that uses magnets and no ionizing radiation in creating images that provide clear contrast between soft and dense tissues. MRI provides a level of clarity that may not be obtainable by routine x-ray.

Post-Approval Studies: Studies conducted as conditions of approval after the device receives FDA authorization to begin marketing. Post-approval studies provide a means for data collection from a large population over an extended period of time.

Reconstruction: A surgical procedure 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. The first time a breast implant is placed for reconstruction, it is called primary reconstruction. All subsequent times the implant is replaced, it is called revision reconstruction.

Reoperation: Any additional surgical procedure performed on the breast and/or implant after initial breast implantation.

Rupture: Specifically associated with silicone gel-filled breast implants, it represents the condition whereby there is a tear or hole in the implant's outer shell.

Saline-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with saline as the filler.

Silicone Gel-Filled Breast Implant: A device intended to be implanted in the breast area of the body to replace or supplement natural breast tissue. Composition includes a silicone outer layer with a silicone gel filler.

Toxic Shock Syndrome (TSS): A collection of signs and symptoms resulting from infection, often caused by Staphylococcal or Streptococcal bacteria. TSS is both rare and potentially life-threatening.

XIV. Data Tables

TABLE 1. Status of Allergan Natrelle and Mentor MemoryGel silicone gel-filled breast implant post-approval studies.

Study	Allergan		Mentor	
	Enrollment	**Follow Up**	**Enrollment**	**Follow Up**
Core Study	715 patients Enrollment Closed	At 10 years: Overall 65% Primary Aug. 66% Rev Aug. 64% Primary Recon. 75% Rev Recon. 80%	1008 patients Enrollment Closed	At 8 years: Overall 58% Primary Aug. 54% Rev Aug. 59% Primary Recon. 67% Rev Recon. 64%
Large Study	41,342* silicone patients (105% of target) and 15,646 saline patients (103% of target). Enrollment Closed	Below Target: 60.5% at year 2 for silicone; 45.1% at year 2 for saline	41,419** silicone patients (98.6% of target) and 1,030 saline patients (103% of target). Enrollment Closed	Below Target: 21.1% at year 3.for silicone; 9.6% at year 3 for saline
Device Failure Studies	Not Applicable***	No follow-up but study reports are due annually	Not Applicable***	No follow-up but study reports are due annually
Focus Group Study	52 patients Enrollment Closed	No Follow-up of Participants	35 patients Enrollment Closed	No Follow-up of Participants
Informed Decision Process Study	Annual Random Sample of 50 Physicians	No Follow-up of participants	Annual Random Sample of 50 Physicians	No Follow-up of participants
Adjunct Study****	Enrollment Closed	54% at 1-year 30% at 3-year 23% at 5-year	Enrollment Closed	36% at 1-year 24% at 3-year 16% at 5-year

* The enrollment for the Allergan *Large Study* silicone group includes at least 97 women in the augmentation cohorts who are younger than 22 years of age.

**The enrollment for the Mentor *Large Study* silicone group excludes 556 women in the augmentation cohorts who are younger than 22 years of age.

***No enrollment targets were set for the *Device Failure Studies*; all explanted and returned devices are included in these studies.

****The protocols for the *Adjunct Studies* did not include follow-up targets.

TABLE 2. Enrollment in the silicone gel-filled breast implant *Core Studies* by manufacturer and indication.

Company	Study Population	Primary Augmen-tation	Revision Augmen-tation	Primary Recon-struction	Revision Recon-struction	Total
Allergan	Overall	455	147	98	15	715
	MRI cohort	147	49	50	5	251
Mentor	Overall	552	145	251	60	1,008
	MRI cohort	202	56	134	28	420

TABLE 3. *Core Study* complications and adverse outcomes over 10 years post-implantation for Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Asymmetry	3.3% (2.0-5.1)	6.5% (3.2-12.8)	23.2% (15.4-33.9)	6.7% (0.2-31.9)
Breast pain	10.9% (8.2-14.3)	11.7% (7.1-18.9)	6.8% (2.8-16.1)	0%
Breast/skin sensation changes	1.6% (0.8-3.3)	2.2% (0.7-6.6)	0%	0%
Bruising	0.4% (0.1-1.8)	3.0% (1.1-7.8)	1.0% (0.1-7.1)	6.7% (0.2-31.9)
Capsular contracture (Baker III/IV)	19.1% (15.6-23.3)	27.5% (20.3-36.6)	24.6% (16.2-36.2)	6.7% (0.2-31.9)
Delayed wound healing	1.1% (0.5-2.7)	0.7% (0.1-4.8)	1.0% (0.1-7.2)	0%
Hematoma	1.6% (0.7-3.2)	2.1% (0.7-6.3)	1.5% (0.2-10.4)	0%
Implant malposition	6.3% (3.9-8.4)	6.0% (3.1-11.7)	2.3% (0.6-8.9)	13.3% (1.7-40.5)
Implant palpability/visibility	1.9% (1.0-3.8)	6.0% (3.0-11.6)	6.5% (0.4-17.0)	6.7% (0.2-31.9)
Implant removal with or without replacement	20.8% (17.2-25.2-)	32.4% (25.0-41.3)	53.8% (43.65.3)	20% (4.3-48.1)
Implant rupture	10.1% (7.4-13.7)	6.3% (2.8-13.7)	27.2% (17.3-41.3)	6.7% (.2-31.9)
Infection	0.5% (0.1-2.1)	1.4% (0.3-5.4)	3.2% (1.0-9.5)	0%
Irritation	0%	0.7% (0.1-5.0)	0%	0%
Necrosis	0.2% (0-1.6%)	0%	2.3% (0.6-8.8)	0%
Nipple complications	6.3% (4.3-9.1)	1.4% (0.3-5.4)	3.3% (1.1-9.8)	0%
Ptosis	2.0% (1.0-3.9)	4.9% (2.2-10.5)	0%	0%
Redness	0.7% (0.2-2.0)	0.8% (0.1-5.2)	2.1% (0.5-8.3)	0%

Table 3 (continued).

Complication or Outcome	Primary Augmentation (N=455)	Revision Augmentation (N=147)	Primary Reconstruction (N=98)	Revision Reconstruction (N=15)
Reoperation	36.1% (31.6-40.9)	46.0% (38.0-54.9)	71.9% (61.5-81.4)	46.7% (21.3-73.4)
Scarring/hypertrophic scarring	4.2% (2.6-6.5)	6.6% (3.5-12.4)	5.5% (2.3-12.7)	0%
Seroma/fluid accumulation	1.8% (0.9-3.5)	6.0% (3.0-11.7)	2.4% (0.3-15.7)	6.7% (0.2-31.9)
Skin rash	0.9% (0.3-2.3)	0.7% (0.1-4.9)	2.1% (0.5-7.9)	6.7% (0.2-31.9)
Swelling	9.2% (6.8-15.0)	8.3% (4.6-14.5)	7.1% (3.5-14.4)	0%
Wrinkling	1.8% (0.8-3.7)	5.4% (2.6-11.0)	10.2% (5.2-19.6)	0%

* The number of patients evaluated at the 10 year follow-up were: 269 (primary augmentation), 74 (revision augmentation), 44 (primary reconstruction), and 8 (revision reconstruction).

TABLE 4. *Core Study* complications and adverse outcomes over 8 years post-implantation for Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis*.

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Breast mass	5.4% (3.7-7.8)	6.5% (3.4-12.0)	5.2% (2.9-9.3)	7.2% (2.8-18.2)
Breast pain	2.5% (1.5-4.3)	3.4% (1.3-8.8)	2.8% (1.2-6.2)	5.2% (1.7-15.3)
Breast/skin sensation changes	2.8% (1.7-4.5)	1.4% (0.4-5.4)	0%	1.8% (0.3-12.0)
Capsular contracture (Baker II)	2.0% (1.1-3.7)	6.2% (3.1-12.1)	4.4% (2.3-8.3)	4.0% (1.0-15.2)
Capsular contracture (Baker III/IV)	10.9% (8.5-13.9)	24.1% (17.7-32.3)	15.3% (11.1-20.9)	23.1% (14.1-36.6)
Delayed wound healing	0%	2.1% (0.7-6.3)	0%	1.7% (0.2-11.3)
Dog ear scars from mastectomy	0%	0%	1.6% (0.6-4.3)	3.4% (0.9-12.8)
Granuloma	0%	2.4% (0.8-7.4)	0%	5.0% (1.6-14.7)
Hematoma	2.9% (1.8-4.8)	2.8% (1.1-7.2)	1.3% (0.4-3.9)	3.4% (0.9-13.0)
Implant extrusion	0%	1.4% (0.4-5.5)	1.2% (0.4-3.7)	1.7% (0.2-11.3)
Implant malposition	0%	2.5% (0.8-7.9)	2.6% (1.2-5.8)	6.7% (2.6-16.9)
Implant removal with or without replacement	7.3% (5.3-9.9)	21.1% (15.0-29.2)	23.3% (18.2-29.4)	29.0% (19.1-42.5)
Implant rupture **	13.6% (7.6-23.6)	15.5% (6.5-34.6)	14.0% (7.6-25.0)	21.3% (7.3-53.3)
Infection	1.6% (0.9-3.1)	1.4% (0.4-5.5)	6.2% (3.8-10.2)	0%
Inflammation of breast	0%	1.4% (0.4-5.5)	0%	1.7% (0.2-11.4)
Lactation difficulties	2.0% (1.1-3.8)	1.6% (0.4-6.1)	0%	0%

Table 4 (continued).

Complication or Outcome	Primary Augmentation (N=552)	Revision Augmentation (N=145)	Primary Reconstruction (N=251)	Revision Reconstruction (N=60)
Metastatic disease	0%	0%	5.7% (3.3-9.6)	4.0% (1.0-15.2)
Miscarriage	2.9% (1.8-4.8)	2.5% (0.8-7.6)	2.3% (1.0-5.6)	0%
New diagnosis of breast cancer	0%	1.8% (0.5-7.2)	1.9% (0.7-5.1)	1.7% (0.2-11.4)
New diagnosis of rheumatic disease	1.8% (1.0-3.5)	1.7% (0.4-6.5)	2.6% (1.1-6.2)	3.4% (0.9-12.9)
Nipple complications	0%	0%	1.3% (0.4-4.1)	0%
Nipple sensation changes	11.8% (9.3-14.8)	14.6% (9.7-21.8)	2.1% (0.9-5.0)	1.7% (0.2-11.3)
Pre-eclampsia at 36 weeks pregnant	0%	1.1% (0.2-7.4)	0%	0%
Reoperation	20.1% (17.0-23.8)	37.8% (30.2-46.6)	38.8% (32.9-45.5)	40.8% (29.5-54.5)
Seroma	1.1% (0.5-2.5)	2.1% (0.7-6.3)	4.8% (2.8-8.4)	1.7% (0.2-11.3)

* The number of patients evaluated at the 10 year follow-up were: 291 (primary augmentation), 77 (revision augmentation), 151 (primary reconstruction), and 36 (revision reconstruction).

** Rupture rates were estimated in MRI cohort at 8 years post-implantation.

TABLE 5. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 10-year follow-up for the Allergan Natrelle silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Allergan	
Complication or Outcome by Study Cohort	**4-year FU Rate (%)**	**10-year FU Rate (%)**
Capsular Contracture		
Primary Augmentation	13.2 (10.0-16.3)	19.1 (15.6-23.3)
Revision Augmentation	17.0 (10.7-23.4)	27.5 (20.3-36.6)
Primary Reconstruction	14.1 (7.0-21.2)	24.6 (16.2-36.2)
Revision Reconstruction	6.7 (0.2-31.9)	6.7 (0.2-31.9)
Reoperation		
Primary Augmentation	23.5 (19.5-27.5)	36.1 (31.6-40.9)
Revision Augmentation	35.3 (27.3-43.4)	46.0 (38.0-54.9)
Primary Reconstruction	40.9 (31.0-50.8)	71.9 (61.5-81.4)
Revision Reconstruction	33.3 (11.8-61.6)	46.7 (21.3-73.4)
Removal		
Primary Augmentation	9.6 (6.8-12.4)	20.8 (17.2-25.2)
Revision Augmentation	13.3 (7.6-19.0)	32.4 (25.0-41.3)
Primary Reconstruction	24.8 (15.9-33.6)	53.8 (43.65.3)
Revision Reconstruction	0	20.0 (4.3-48.1)

TABLE 6. Comparison of rates of key complications and outcomes in the *Core Studies* at the time of approval and at the 8-year follow-up for the Mentor MemoryGel silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time and 95% confidence intervals calculated using Kaplan-Meier analysis.

	Mentor	
Complication or Outcome by Study Cohort	**3-year FU Rate (%)**	**8-year FU Rate (%)**
Capsular Contracture		
Primary Augmentation	8.1 (5.8-10.4)	10.9 (8.5-13.9)
Revision Augmentation	18.9 (12.5-25.4)	24.1 (17.7-32.3)
Primary Reconstruction	8.3 (4.7-11.9)	15.3 (11.1-20.9)
Revision Reconstruction	16.3 (5.0-27.6)	23.1 (14.1-36.6)
Reoperation		
Primary Augmentation	15.4 (12.3-18.4)	20.1 (17.0-23.8)
Revision Augmentation	28.0 (20.4-35.6)	37.8 (30.2-46.6)
Primary Reconstruction	27.0 (21.4-32.6)	38.8 (32.9-45.5)
Revision Reconstruction	29.1 (17.4-40.7)	40.8 (29.5-54.5)
Removal		
Primary Augmentation	4.9 (3.1-6.7)	7.3 (5.3-9.9)
Revision Augmentation	13.4 (7.5-19.3)	21.1 (15.0-29.2)
Primary Reconstruction	12.7 (8.5-16.9)	23.3 (18.2-29.4)
Revision Reconstruction	13.7 (4.9-22.6)	29.0 (19.1-42.5)

TABLE 7. Primary reasons for implant removal for Allergan Natrelle silicone gel-filled breast implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=156*)	Revision Augmentation (N=78*)	Primary Reconstruction (N=56*)	Revision Reconstruction (N=3*)
Asymmetry	7 (4.5%)	1 (1.3%)	12 (21.4%)	2 (66.7%)
Breast cancer mass	2 (1.3%)	2 (2.6%)	0	0
Breast pain	5 (3.2%)	1 (1.3%)	0	0
Breast tissue contour Deformity	1 (0.6%)	0	0	0
Capsular contracture	50 (32.1%)	28 (35.9%)	10 (17.9%)	1 (33.3%)
Hematoma/seroma	0	0	1 (1.8%)	0
Implant extrusion	1 (0.6%)	1 (1.3%)	1 (1.8%)	0
Implant malposition	11 (7.1%)	14 (18.0%)	11 (19.6%)	0
Implant rupture	27 (17.3%)	6 (7.7%)	15 (26.8%)	0
Infection	2 (1.3%)	2 (2.6%)	0	0
Necrosis	0	0	1 (1.8%)	0
Need for biopsy	1 (0.6%)	0	0	0
Patient request for style/size change	31 (19.9%)	11 (14.1%)	4 (7.1%)	0
Ptosis	12 (7.7%)	6 (7.7%)	0	0
Scarring	0	2 (2.6%)	0	0
Wrinkling/rippling	6 (3.9%)	2 (2.6%)	1 (1.8%)	0

* Total number of implant removals in each cohort.

TABLE 8. Primary reasons for implant removal for Mentor MemoryGel silicone gel-filled breast implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for removal and the percentage of the total number of reasons for removal within each cohort.

Reason for Removal	Primary Augmentation (N=68*)	Revision Augmentation (N=51*)	Primary Reconstruction (N=74*)	Revision Reconstruction (N=2*)
Asymmetry	1 (1.5%)	2 (3.9%)	15 (20.3%)	3 (13.6%)
Breast pain	3 (4.4%)	0	2 (2.7%)	1 (4.5%)
Capsular contracture (Baker II/III/IV)	13 (19.1%)	15 (29.4%)	11 (14.9%)	5 (22.7%)
Hematoma	0	0	1 (1.4%)	0
Infection	2 (2.9%)	1 (2.0%)	2 (2.7%)	0
Implant Extrusion	0	1 (2.0%)	2 (2.7%)	1 (4.5%)
Implant malposition	0	0	4 (5.4%)	0
Implant rupture	3 (4.4%)	4 (7.8%)	8 (10.8%)	1 (4.5%)
Necrosis	2 (2.9%)	0	0	0
Patient request for style/size change	36 (52.9%)	18 (35.3%)	17 (23.0%)	5 (22.7%)
Ptosis	0	0	1 (1.4%)	0
Wrinkling	1 (1.5%)	0	0	1 (4.5%)
Other	7 (10.3%)	9 (17.6%)	11 (14.9%)	5 (22.7%)

* Total number of implant removals in each cohort.

TABLE 9. Primary Reasons for Reoperation for Allergan Natrelle Silicone Gel- filled Breast Implants in the *Core Study* through 10 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=221**)	Revision Augmentation (N=108**)	Primary Reconstruction (N=93**)	Revision Reconstruction (N=12**)
Asymmetry	5 (2.3%)	3 (2.8%)	15 (16.1%)	2 (16.7%)
Breast cancer mass	4 (1.8%)	3 (2.8%)	3 (3.2%)	0
Breast pain	3 (1.4%)	1 (0.9%)	0	0
Breast tissue contour Deformity	0	1 (0.9%)	2 (2.2%)	0
Capsular contracture	55 (24.9%)	26 (24.1%)	12 (12.9%)	2 (16.7%)
Delayed wound healing	3 (1.4%)	2 (1.9%)	1 (1.1%)	0
Device injury -- iatrogenic or traumatic	0	1 (0.9%)	0	0
Extrusion	1 (0.5%)	1 (0.9%)	2 (2.2%)	0
Hematoma/seroma	13 (5.9%)	13 (12.0%)	8 (8.6%)	0
Implant malposition	27 (12.2%)	12 (11.1%)	15 (16.1%)	0
Implant palpability/visibility	1 (0.5%)	1 (0.9%)	0	0
Implant rupture	29 (13.1%)	7 (6.5%)	14 (15.1%)	0
Infection	2 (0.9%)	3 (2.8%)	0	0
Necrosis	1 (0.5%)	0	1 (1.1%)	0
Need for biopsy	28 (12.7%)	9 (8.3%)	8 (8.6%)	1 (8.3%)
Nipple complications	1 (0.5%)	3 (2.8%)	1 (1.1%)	5 (41.7%)
Patient request for style/size change	12 (5.4%)	3 (2.8%)	3 (3.2%)	0
Ptosis	25 (11.3%)	9 (8.3%)	4 (4.3%)	1 (8.3%)
Scarring	8 (3.6%)	7 (6.5%)	3 (3.2%)	1 (8.3%)
Wrinkling/rippling	3 (1.4%)	2 (1.9%)	1 (1.1%)	0

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 10. Primary Reasons for Reoperation for Mentor MemoryGel Silicone Gel-filled Breast Implants in the *Core Study* through 8 years. Table shows the number of times the reason was reported as the primary reason for reoperation and the percentage of the total number of reasons for reoperation within each cohort.

Reason for Reoperation*	Primary Augmentation (N=146**)	Revision Augmentation (N=78**)	Primary Reconstruction (N=123**)	Revision Reconstruction (N=38**)
Asymmetry	5 (3.4%)	1 (1.3%)	20 (16.3%)	2 (5.3%)
Abnormal screening	1 (0.7%)	0	0	0
Breast cancer	0	1 (1.3%)	1 (0.8%)	0
Breast mass	13 (8.9%)	9 (11.5%)	14 (11.4%)	7 (18.4%)
Breast pain	1(0.7%)	0	2 (1.6%)	1 (2.6%)
Capsular contracture (Baker II/III/IV)	44 (30.1%)	24 (30.8%)	18 (14.6%)	5 (13.2%)
Calcification	2 (1.4%)	0	0	0
Capsular tear	1 (0.7%)	0	0	1 (2.6%)
Delayed wound healing	1 (0.7%)	5 (6.4%)	0	0
Extrusion/Necrosis	2 (1.4%)	2 (2.6%)	2 (1.6%)	1 (2.6%)
Hematoma/Seroma	12 (8.2%)	5 (6.4%)	4 (3.2%)	1 (2.6%)
Implant malposition	4 (2.7%)	1 (1.3%)	8 (6.5%)	0
Implant rupture	2 (1.4%)	4 (5.1%)	10 (8.1%)	1 (2.6%)
Infection	3 (2.1%)	1 (1.3%)	3 (2.4%)	0
Nipple complications	0	0	1 (0.8%)	0
Patient request for style/size change	20 (13.7%)	11 (14.1%)	11 (8.9%)	4 (10.5%)
Ptosis	4 (2.7%)	2 (2.6%)	4 (3.3%)	3 (7.9%)
Scarring/hypertrophic scarring	16 (11.0%)	3 (3.8%)	4 (3.3%)	0
Suture complication	1 (0.7%)	0	1 (0.8%)	0
Wrinkling/rippling	1 (0.7%)	1 (1.3%)	0	1 (2.6%)

* When reoperations were performed for multiple reasons, a hierarchy was used to determine the primary reason.

** Total number of reoperations in each cohort.

TABLE 11. Allergan *Large Post-Approval Study* of Natrelle silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,342)	Saline (N=15,646)	Total Number of Participants (N=56,988)
Primary Augmentation*	29,886 (72.3%)	14,447 (92.3%)	44,333 (77.8%)
Revision Augmentation	6,033 (14.6%)	970 (6.2%)	7,003 (12.3%)
Primary Reconstruction	4,714 (11.4%)	184 (1.2%)	4,898 (8.6%)
Revision Reconstruction	709 (1.7%)	44 (0.3%)	753 (1.3%)
Missing	0	1 (<0.1%)	1 (<0.1%)

* Allergan is still in the process of examining and reporting the number of augmentation patients younger than 22 years of age. The augmentation numbers listed in this table include at least 97 women who were younger than the qualifying age for this study (22 or older).

TABLE 12. Mentor *Large Post-Approval Study* of MemoryGel silicone gel-filled breast implants: summary of enrolled participants by indication. Table shows the number of participants in each cohort and the percentage that each cohort contributes to the total number of participants for each implant type.

Indication	Silicone (N=41,975)	Saline (N=1,030)	Total Number of Participants (N=43,005)
Primary Augmentation	26,118 (62.2%)	930 (90.3%)	27,048 (62.9%)
Revision Augmentation	8,365 (19.9%)	76 (7.4%)	8,441 (19.6%)
Primary Reconstruction	5,031 (12.0%)	13 (1.3%)	5,042 (11.7%)
Revision Reconstruction	1,757 (4.2%)	9 (0.9%)	1,766 (4.1%)
Missing	148 (0.4%)	2 (0.2%)	150 (0.3%)
Augmentation patients younger than age 22	556 (1.3%)	0 (0%)	556 (1.3%)

TABLE 13. Primary reason for explantation for Allergan Natrelle silicone gel-filled breast implants in the *Large Post-Approval Study* (by implant). Investigator reports contain numbers reported by physicians after clinical evaluation. Patient reports come from patient survey data.

Reason for Explantation	Number of Explants (Investigator Report at Year 1) (N=1310*)	Number of Explants (Patient Report at Year 1) (N=926*)	Number of Explants (Patient Report at Year 2) (N=350*)
Suspected rupture	35 (2.7%)	25 (2.3%)	15 (4.3%)
Infection	79 (6.0%)	78 (8.4%)	27 (7.7%)
Capsular contracture	128 (9.8%)	184 (19.9%)	77 (22.0%)
Implant malposition	119 (9.1%)	110 (11.9%)	48 (13.7%)
Ptosis	38 (2.9%)	69 (7.5%)	13 (3.7%)
Desire for size/style change	664 (50.7%)	299 (32.3%)	118 (33.7%)
Other	247 (18.9%)	161 (17.4%)	52 (14.9%)

* Total number of implant removals.

TABLE 14. Primary reason for explantation during 3 years after implantation for Mentor MemoryGel silicone gel-filled breast implants in the *Large Post-Approval Study*.

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
Asymmetry	21 (5.0%)	39 (13.3%)	108 (23.8%)	37 (25.5%)
Capsular contracture (Baker II/III/IV)	14 (3.3%)	16 (5.5%)	21 (4.6%)	6 (4.1%)
Capsular tear	0	0 (0.0%)	2 (0.4%)	0
Implant palpability	2 (0.5%)	1 (0.3%)	0	0
Implant removal	5 (1.2%)	7 (2.4%)	2 (0.4%)	3 (2.1%)
Implant rupture	7 (1.7%)	12 (4.1%)	2 (0.4%)	0
Lack of projection	0	6 (2.0%)	12 (2.6%)	3 (2.1%)
Position change (dissatisfaction)	3 (0.7%)	0 (0.0%)	4 (0.9%)	3 (2.1%)
Ptosis	1 (0.2%)	1 (0.3%)	2 (0.4%)	0
Size change – patient request	169 (40.2%)	91 (31.1%)	92 (20.3%)	18 (12.4%)
Size change – physician assessment	5 (1.2%)	2 (0.7%)	20 (4.4%)	4 (2.8%)
Symmastia	0	0	2 (0.4%)	0
Wrinkling	2 (0.5%)	3 (1.0%)	9 (2.0%)	4 (2.8%)
Breast pain not associated with other complications	3 (0.7%)	2 (0.7%)	4 (0.9%)	2 (1.4%)
Extrusion	11 (2.6%)	14 (4.8%)	32 (7.0%)	9 (6.2%)
Necrosis	0	0	3 (0.7%)	0
Hematoma	1 (0.2%)	1 (0.3%)	0	0
Irritation/Inflammation	3 (0.7%)	0	0	0
Seroma	1 (0.2%)	7 (2.4%)	1 (0.2%)	1 (0.7%)
Infection	37 (8.8%)	23 (7.8%)	34 (8.2%)	9 (6.7%)
New diagnosis of Breast cancer	1 (0.2%)	0	2 (0.4%)	0

Table 14 (continued).

Reason for Removal	Primary Augmentation (N=420*)	Revision Augmentation (N=293*)	Primary Reconstruction (N=454*)	Revision Reconstruction (N=145*)
New diagnosis of rheumatic disease	0	0	1 (0.2%)	0
Unknown	131 (31.2%)	76 (25.9%)	113 (24.9%)	52 (35.9%)
Other	14 (3.3%)	13 (4.4%)	5 (1.1%)	1 (0.7%)

* Total number of implant removals

TABLE 15. MDR reports of patient problems (based on Patient Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Patient Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=530)
1	Surgical Procedure (generally replacement or removal)	78	15.7
2	Pain	66	12.5
3	Rash/hives/itching/burning sensation	36	6.8
4	Capsular Contracture	33	6.2
5	Therapy/non-surgical treatment	26	4.9
6	Fatigue/weakness	25	4.7
7	Arthralgia/arthritis/myalgia	22	4.2
8	Swelling/edema	22	4.2
9	Palpitations/chest pain	15	2.8
10	Scarring/numbness	14	2.8
11	Disability	9	1.7
12	Infection	9	1.7
13	Breathing difficulties	9	1.7

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 530 "Patient Problem Codes" were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 16. MDR reports of device problems (based on Device Problem Codes) with silicone gel-filled breast implants, ranked by frequency of reporting.*

Rank	Device Problem Code Reported**	Number of Times the Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=239)
1	Implant removed (both to treat complications and remove at woman's request to change implant size or shape)	70	30.1
2	Rupture	62	26.0
3	Implant replaced	36	15.0
4	Device or device fragment remains in patient	24	10.1
5	Sterility/foreign material	4	1.7
6	Migration of device or device component	3	1.3
7	Implant Extrusion Displacement/Malposition of device	3	1.3

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 239 patient problem codes were used in 133 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. For reports required by FDA, the reporter assigns the patient and device problem codes.

TABLE 17. PSR reports of patient problems (based on Patient Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Patient Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=26,511)
1	Surgical Procedure	7,800	29.4
2	Capsular Contraction	4983	18.8
3	Pain	2695	10.2
4	Infection	1,001	3.8
5	Breast lumps	990	3.7
6	Reynaud's phenomenon	364	1.4
8	Inflammation	341	1.3
9	Cancer, Other	331	1.2
10	No consequence to patient	313	1.2
11	Wrinkling	312	1.2
	Other	2558	9.6
	Patient condition unknown	4823	18.2

* Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple patient problem codes. A total of 26,511 patient problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

At the time PSR was authorized, the agency defined the types of events that could be submitted under the PSR program and provided the silicone gel-filled breast implants manufacturers with a set of specific patient problem codes and device problem codes to be used for PSR reports. Like all coding systems, accuracy and reliability of coded information depends on the correct assignment of the codes.

TABLE 18. PSR reports of device problems (based on Device Problem Code frequency of 1% or greater) with silicone gel-filled breast implants.* Ranked by frequency of reporting.

Rank	Device Problem Code**	Number of Times Problem Code was Used	Percent of the Total Number of Problem Codes Used (N=12,327)
1	Device-patient incompatibility	4860	39.4
2	Rupture	4541	36.8
3	Malposition	903	7.3
4	Tears, rips, holes in devices or device material (device never implanted), out of box failure	244	3.1
5	Wrinkling or folds	288	2.3
6	Visibility or palpability	200	1.6
	Other	1157	9.4

*Reporting period: November 17, 2006 to December 31, 2010

** One report may contain multiple device problem codes. A total of 12,327 device problem codes were used in 16,681 reports. Coding of reports increases the ability to accurately collect, categorize, and compare information within and across reporting and data collection systems. This facilitates the analysis of potential safety and effectiveness issues and the assessment of trends within a product category.

At the time PSR was authorized, the agency defined the types of events that could be submitted under the PSR program and provided the silicone gel-filled breast implants manufacturers with a set of specific patient problem codes and device problem codes to be used for PSR reports. Like all coding systems, accuracy and reliability of coded information depends on the correct assignment of the codes.