

Executive Summary
Silicone Gel-Filled Breast Implants
General Issues Panel
August 30-31, 2011



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I. Background

a. Purpose of the Panel Meeting

The purpose of this panel meeting is to discuss strategies to evaluate the real-world and long term performance of silicone gel-filled breast implants after market approval. FDA will update the panel on the status of the ongoing post-approval studies and will seek recommendations from the panel on improving the design and implementation of silicone gel-filled breast implant post-approval studies and surveillance for the ongoing silicone gel-filled breast implant post-approval studies and future post-approval studies for premarket submissions seeking the approval of new silicone gel-filled breast implants. The goal of this discussion is to identify approaches that will maximize the feasibility and successful completion of mandated postmarket studies. Additionally, we seek input on innovative approaches to both mandated postmarket studies and surveillance approaches that have a high probability of yielding valid and meaningful data on long-term performance and safety.

The FDA approved the Allergan and Mentor silicone gel-filled breast implants for marketing in the United States in 2006 for breast reconstruction for women of any age and breast augmentation for women at least age 22. When the FDA approved both devices it recognized that there were limited data on rare events and long-term outcomes. In order to better understand the real-world and long-term performance of these devices and to monitor for previously unrecognized adverse events, the FDA required the manufacturers to conduct post-approval studies. Despite a conclusion in a 1999 report by the Institute of Medicine (Appendix A), concerns related to systemic health problems led the FDA to mandate post-approval studies that had sufficient power to detect rare events. These studies sought to enroll over 40,000 patients each and follow them for ten years. The study protocols (Appendix B and Appendix C) and the original conditions of approval and changes over time are summarized in Table 1 below.

| Table 1: Original Key Conditional PAS Components^S Of Approval For Both Allergan And Mentor Silicone Gel Filled Breast Implants And Subsequent FDA Approved Changes To PAS Protocol | | |
|--|--|-----------------------------------|
| PAS Study | Original Condition of Approval | Changes in Study Protocol* |
| Allergan | | |
| Core | <p>Design-10 year multi-center prospective of 4 cohorts defined by indication for breast implant</p> <p>Purpose- document the safety and effectiveness of Silicone-Filled Breast Implants as indicated for breast augmentation, breast reconstruction, or breast implant revision in existing Core IDE study pt</p> <p>Sample size-715</p> <p>Endpoints-</p> <p>Effectiveness:</p> <ul style="list-style-type: none"> • Circumferential chest size change • Bra cup size change (augmentation patients only) • Patient satisfaction | none |

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| | <ul style="list-style-type: none"> Quality of life (QoL). QoL is comprised of measures of self-esteem, body image, and general health outcome. <p>Safety:</p> <ul style="list-style-type: none"> Complication rates Reasons for re-operation Reasons for implant removal <p>Study Hypothesis-none</p> <p>Data Collection- FU 6 months, 1 yr, 2 yrs, and annually through 10 yrs post-implant. Rupture assessed for pts by MRI at yr 1,3,5,7 and 9 yrs for silent rupture.</p> | |
| Large | <p>Design-10 year multi-center prospective cohort of newly recruited patients</p> <p>Purpose- address specific issues for which the Core Study was not designed to fully answer, as well as to provide a real-world assessment of some endpoints</p> <p>Sample size-39,390 Allergan silicone gel patients and 19,605 saline-filled breast implant patients as the control group.</p> <p>Endpoints- long-term local complications, connective tissue disease (CTD), CTD signs and symptoms, neurological disease, neurological signs and symptoms, offspring issues, reproductive issues, lactation issues, cancer, suicide, mammography issues, and MRI compliance and rupture results.</p> <p>Study Hypothesis-Compare rates of rare AEs between silicone gel to saline controls</p> <p>Data Collection- Annual pt questionnaires, and physician evaluations yr 1,4,10</p> | Sample size - Saline-filled implant control size reduced from 19,605 to 15,240 |
| Device Failure | <p>Design-Continued preclinical studies of long-term modes and causes of failure</p> <p>Purpose- Better understand possible modes of gel implant failure in vivo</p> <p>Sample size-none, all returned devices analyzed</p> <p>Endpoints- 1)Implant status: Intact and functional, Device surface observation, Gel related observations, Failure (device has opening in the shell) 2) Primary Failure mode (Failed devices only) 3) Final Laboratory Analysis Conclusion</p> <p>Study Hypothesis-none</p> <p>Data Collection- device identification, device analysis, data review and summary</p> | none |
| Informed Decision Process | <p>Design-cross sectional annual survey</p> <p>Purpose- to assess the success of the Informed Decision Process. The Informed Decision Process evaluation survey uses a cross-sectional study design</p> <p>Sample size-random sample of 50 physicians who implant</p> | none |

| | | |
|----------------|--|--|
| | <p>Allergan’s Natrelle Silicone-filled breast implant</p> <p>Endpoints- none</p> <p>Study Hypothesis-none</p> <p>Data Collection- 50 randomly selected physicians on annual basis until FDA informs sponsor survey summary no longer necessary</p> | |
| Adjunct | <p>Design-follow up of single arm cohort followed for 5 yr post surgery</p> <p>Purpose- provide additional data assessing local complications associated with the device</p> <p>Sample size-women who received device while undergoing reconstruction between 1998 and 2006 (reconstruction and revision only) reconstruction: 44,883 pts, revision: 39,198</p> <p>Endpoints- Complications (e.g., device rupture, capsular contracture), reoperations involving the breast/chest area (e.g., implant replacement/removal)</p> <p>Study Hypothesis-none</p> <p>Data Collection- FU intervals of 1,3 and 5 yr post implant and unscheduled visits that collect safety data</p> | none |
| Mentor | | |
| Core | <p>Design-10 year multi-center open prospective study</p> <p>Purpose- document the safety and effectiveness of MemoryGel Breast Implants as indicated for breast augmentation, breast reconstruction, or breast implant revision in</p> <p>Sample size-1,008 pt with 420 in MRI sub-study</p> <p>Endpoints-</p> <p>Effectiveness:</p> <ul style="list-style-type: none"> • Circumferential chest size change • Bra cup size change (augmentation patients only) • Patient satisfaction • Quality of life (QoL). QoL is comprised of measures of self-esteem, body image, and general health outcome. <p>Safety:</p> <ul style="list-style-type: none"> • Complication rates • Time to occurrence of complication <p>Study Hypothesis-none</p> <p>Data Collection- FU 6 months, 1 yr through 10 yrs post-implant. Rupture assessed for pts by MRI at yr 1,2,4 for pts in MRI sub-group and measured by MRI at 6,8 and 10 for all other pts.</p> | <p>Data Collection:</p> <p>All pts undergo MRI scan at 6,8,10 yrs post surgery.</p> |
| Large | <p>Design-10 year multi-center prospective cohort of newly recruited patients</p> <p>Purpose- address specific issues for which the Core Study was not designed to fully answer, as well as to provide a</p> | <p>Design- PAS allows for voluntary rather than mandatory</p> |

| | | |
|----------------------------------|---|---|
| | <p>real-world assessment of some endpoints</p> <p>Sample size-41,900 Mentor MemoryGel patients and 1,000 saline-filled breast implant patients as the control group.</p> <p>Endpoints- long-term local complications, connective tissue disease (CTD), CTD signs and symptoms, neurological disease, neurological signs and symptoms, offspring issues, reproductive issues, lactation issues, cancer, suicide, mammography issues, and MRI compliance and rupture results.</p> <p>Study Hypothesis-Compare rates of rare AEs between MemoryGel to saline controls</p> <p>Data Collection- Annual pt questionnaires, and physician evaluations at yr 1, between 4-6 yr and between 9-10 yr and any unscheduled visits</p> | <p>study participation of all patients, irrespective of type of implant</p> <p>Sample size- concurrent control participants enrolled by approximately 30 physicians who routinely use saline implants to increase enrollment numbers</p> |
| Device Failure | <p>Design-Continued preclinical studies of long-term modes and causes of failure</p> <p>Purpose- Better understand possible modes of gel implant failure in vivo</p> <p>Sample size-none, IDE Core devices analyzed</p> <p>Endpoints- 1)Implant status: Intact and functional, Device surface observation, Gel related observations, Failure (device has opening in the shell) 2) Primary Failure mode (Failed devices only)</p> <p>3) Final Laboratory Analysis Conclusion</p> <p>Study Hypothesis-none</p> <p>Data Collection- device identification, device analysis, data review and summary</p> | <p>Data Collection- Mentor performs mechanical testing on all returned devices not just IDE Core Study devices</p> |
| Informed Decision Process | <p>Design-cross sectional annual survey</p> <p>Purpose- to assess the success of the Informed Decision Process. The Informed Decision Process evaluation survey uses a cross-sectional study design</p> <p>Sample size-random sample of 50 physicians who implant Mentor’s MemoryGel-filled breast implant</p> <p>Endpoints- none</p> <p>Study Hypothesis-none</p> <p>Data Collection- 50 randomly selected physicians on annual basis until FDA informs sponsor survey summary no longer necessary</p> | <p>Data Collection: 6 question items on the survey were modified based on FDA recommendations</p> |
| Adjunct | <p>Design-follow up of single arm cohort followed for 5 yr post surgery</p> <p>Purpose- provide additional data assessing local complications associated with the device</p> <p>Sample size-women who received device while undergoing</p> | <p>none</p> |

| | | |
|---|--|--|
| | reconstruction between 1992 and 2006 (reconstruction and revision only); reconstruction and revision pts 124,371 Endpoints- Complications (e.g., device rupture, capsular contracture), reoperations involving the breast/chest area (e.g., implant replacement/removal) and satisfaction of implant Study Hypothesis- none Data Collection- FU intervals of 1,3 and 5 yr post implant and unscheduled visits that collect safety data | |
| *Only highlights major changes to the PAS protocol that were agreed upon with FDA, all other elements presented in the original condition of approval have remained the same. § The Focus Group studies as mandated by the condition of approval are not presented in this table as it was a one time study with no interim reports submitted to the FDA FU=Follow-up Pt=Patient | | |

Findings on the first 3-4 years of the Core Studies are summarized in each company’s respective “Summary of Safety and Effectiveness Data” (Appendix D and E).

Information on the status of the current clinical studies (Core and Large) and the challenges that have been encountered in both enrollment and long-term follow-up are summarized in this document and the paper contained in Appendix F, and will be discussed at this meeting. Both FDA and the companies of the currently approved silicone gel-filled breast implants will present information regarding the current status of these studies.

This meeting will address the challenges in the current post-approval studies and potential enrollment strategies and design methodologies that would be successful in future post-approval studies mandated by the FDA to address unanswered postmarket questions about the real world and long-term performance of future breast implants.

The panel will be asked to discuss current and future post-approval study designs, specifically optimal methodologies for the endpoints of interest, the roles of registries, the types of studies that are needed, important outcomes to evaluate and the most appropriate comparators.

b. FDA Update June 22, 2011

Silicone gel-filled breast implants were introduced to the U.S. in 1962. After a number of regulatory actions, including a moratorium on marketing of silicone gel-filled breast implants in 1992, the FDA approved Allergan’s* Natrelle Silicone Gel-Filled Breast Implants and Mentor’s MemoryGel Silicone Gel-Filled Breast Implants in November 2006. The full details of the regulatory history can be found at the FDA Breast Implant website,

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

<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm064461.htm>.

At a panel meeting held prior to these approvals, FDA promised to give an update of the status of the postapproval studies in five years. On June 22, 2011, the FDA followed through on this promise with a white paper (Appendix F), an updated website and other materials, and media and stakeholder calls.

II. Status of Current PAS

a. Enrollment

The current status of enrollment of each PAS is presented here. Full details of the all PAS findings can be found in the document “FDA Update on the Safety of Silicone Gel-Filled Breast Implants, June 2011” (referred to as the “white paper” for the remainder of this document, please see Appendix F).

i. Core Studies

The Allergan *Core Study* enrolled 715 patients and the Mentor *Core Study* enrolled 1,008 patients. Based on the 2010 annual report, the preliminary follow-up rates at 10 years post-implant are 65 percent for Allergan, and at 8 years post-implant are 58 percent for Mentor. 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 ineligible for follow-up because they had died or discontinued participation. While manufacturers continued to collect information on women who had their breast implants removed, these women no longer contributed to new data for the statistical analyses. The FDA has asked both companies to intensify their efforts to increase follow-up rates. Final results should be available in 2012, after all patients have been followed for 10 years.

ii. Large Studies

To ensure timely enrollment of study subjects and fulfill the conditions of approval for these two implants, FDA required each company to establish an enrollment rate plan for its PAS. Both companies agreed to complete patient enrollment during the first 2 years of their large post-approval study. Each company also set benchmarks for enrolling participants to achieve distributions by implant type, ethnicity and indication for breast implants that are representative of the population of women who receive breast implants. Allergan and Mentor also specified their strategies for monitoring and tracking subject enrollment and correcting enrollment imbalances in a timely manner.

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 its *Large Study* in February 2007 as required by the approval order 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. Mentor 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.

Among *Large Study* participants, 97 women enrolled in the Allergan study and 556 women enrolled in the Mentor study who received breast implants for augmentation were under age 22, which did not meet the enrollment criteria and are off label use. The tables below for Allergan’s data include these patients. The tables for Mentor’s data include only the 41,419 patients who met the original enrollment criteria.

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. Mentor completed enrollment in 29 months, 11 months later than projected.

Allergan encountered more difficulties with enrollment and FDA met with Allergan in February 2008 to discuss the slow enrollment rates and Allergan’s plans for accelerating enrollment. Allergan cited several challenges in meeting FDA enrollment for the Large PAS and proposed a number of strategies to improve physician and patient enrollment and to work to identify and implement strategies to close the gap between the enrollment targets and actual enrollment and successfully completed enrollment after 44 months.

The details of enrollment are presented in Tables 1 and 2.

| Study Months | Original Projected | Revised Projected | Actual |
|---------------------|---------------------------|--------------------------|---------------|
| 6 months | 4,130 (7%) | 3,824 (7%) | 1,674 (3%) |
| 12 months | 18,289 (31%) | 16,935 (31%) | 14,000 (26%) |
| 18 months | 35,987 (61%) | 33,324 (61%) | 28,988 (53%) |
| 24 months | 58,995 (100%) | 54,630 (100%) | 39,237 (71%) |
| 36 months | | | 54,512 (96%) |
| 44 months | | | 56,988 (104%) |

| Study Months | Projected | Actual |
|---------------------|------------------|---------------|
| 6 months | 14,300 | 14,686 (34%) |
| 12 months | 28,600 | 28,204 (66%) |
| 18 months | 42,900 | 39,702 (92%) |
| 29 months | | 43,005 (100%) |

The panel will be asked to discuss methodologies and enrollment strategies that would be successful in future post-approval studies mandated by the FDA to address unanswered postmarket questions about the real world and long-term performance of

iii. Racial and Ethnic Distribution in Large Studies

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. Both studies have included an adequate racial distribution that is reflective of the United States population.

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.

b. Follow-up in the Large PAS Studies

Follow-up rates reported to the FDA in the 2010 *Large Study* progress reports remain below targets, however some improvement has been noted for Allergan. 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. Full details of enrollment can be found in the white paper (Appendix F).

The 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.

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.

Follow-up rates by indication are presented in Tables 3 and 4.

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

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

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.

i. Strategies to Increase Enrollment

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 (for more information, please follow the link). 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.

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.

The panel will be asked to discuss strategies for maintaining physician and patient compliance with the follow-up schedule in the ongoing and future post-approval studies mandated by the FDA to address unanswered postmarket questions about silicone breast implant. The panel will be asked to consider the unique contributions that various stakeholders—including manufacturers, contract research organizations, FDA, professional societies—can make in implementing these strategies.

c. Compliance with FDA Recommended Schedule for MRI Screening

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 metallic foreign bodies or whose physical size and weight precludes them from having an MRI. Once the decision has been made to remove an implant there is no medical need for an MRI. However, a pre-operative MRI is useful in the FDA-mandated PAS to compare the results of the MRI with the physical evaluation of the explanted device for evidence of rupture.

The schedule for MRI screening for silicone gel-filled breast implant ruptures recommended in FDA-approved labeling was based on the sensitivity and specificity of various imaging modalities in detecting implant ruptures reviewed in the Institute of Medicine's report *Safety of Silicone Breast Implants* and the IOM's conclusion that MRI is "the most sensitive and specific technology for rupture diagnosis" and has the advantage over other imaging modalities of being able to detect intracapsular ruptures. The sections below describe the importance of detecting asymptomatic ruptures, the accuracy of various breast imaging modalities in evaluating loss of implant integrity, including results of two meta-analyses published since the IOM report, and the lessons learned from the Allergan and Mentor Core studies.

i. Silent versus any rupture detection

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.

Silent or asymptomatic ruptures are often unrecognized for many years because they can occur without symptoms or changes in the physical appearance of the breast and they may not be detected by a physical examination or mammogram. This makes it difficult to know when a rupture occurs and estimate the incidence (i.e., the number of implant ruptures that occur during a specific period of time in a specific group of women).

ii. Sensitivity and Specificity of Various Imaging modalities in Rupture Detection

The effectiveness of different imaging modalities in detecting symptomatic and asymptomatic breast implant ruptures has been evaluated including, magnetic resonance imaging (MRI), mammography, ultrasound, and computed tomography (CT). Each modality has specific strengths and weaknesses, and varying sensitivity and specificity reported in the literature.

Magnetic resonance imaging (MRI) can be used to detect both intracapsular and extracapsular ruptures. In the older models of breast implants, MRI can detect more than 90% of ruptures, and fails to detect a rupture less than 10% of the time.¹ 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.²

Mammograms have the ability to detect extracapsular silicone implant ruptures, but is not the preferred method of rupture detection. Because the percentage of extracapsular ruptures with the silicone gel implants is expected to be small relative to intracapsular ruptures, mammograms will miss most of the ruptures. In older models of breast implants, extracapsular ruptures are expected to be only 10-22% of silicone implant ruptures³. If extracapsular silicone is detected by mammography, it could be due to a prior silicone implant rupture (and thereby unrelated to the current silicone implant) or that she received silicone injections previously. Mammogram is an appropriate choice of imaging in the case of extracapsular ruptures. The sensitivity of mammogram for detecting implant ruptures ranges from 11% to 23 % with high specificity varying from 88.7% to 98%^{4 5 6 7}.

¹ Gorczyca DP, Gorczyca SM, Gorczyca KL. The diagnosis of silicone breast implant rupture. *Plast Reconstr Surg.* 2007;120(7 Suppl 1):49S-61S

² Song JW, Kim HM, Bellfi LT, Chung KC. The effect of study design biases on the diagnostic accuracy of magnetic resonance imaging for detecting silicone breast implant ruptures: a meta-analysis. *Plast Reconstr Surg.* 2011;127(3):1029-1044

³ Ibid, Gorczyca 2007.

⁴ Ahn CY, Shaw WW, Narayanan K, Gorczyca D, DeBruhl ND, Bassett LW. Residual silicone detection using MRI following previous breast implant removal: Case reports. *Aesth Plast Surg* 1995; 19: 361-367.

The value of current ultrasound technology to detect intracapsular ruptures is controversial because the accuracy of rupture diagnosis by this imaging technique is dependent on the skill of the ultrasound technologist, the type of equipment used and the experience of the interpreting physician. 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 to silicone injections. However, improvements in high-resolution ultrasound imaging could potentially provide an alternate modality to screen implants.

Computed tomography (CT) can also detect intracapsular silicone implant ruptures, but is limited in its ability to detect extracapsular ruptures. This imaging technique is a useful alternative for women who are unable to have MRIs due to size and weight restrictions of MRI or because they are claustrophobic. A disadvantage of CT scans is that they expose patients to ionizing radiation.

A recent meta-analysis including 13 studies on the diagnostic accuracy of MRI for detecting silicone gel-filled breast implants indicated relatively high accuracy with a pooled sensitivity of 87.0 percent (95% confidence interval, 81 to 91 percent) and a specificity of 89.9 percent (95% confidence interval, 82 to 94 percent)⁸ The sensitivity and specificity in MRI studies that used symptomatic samples were higher (sensitivity, 88 percent; specificity, 94 percent) compared with studies using asymptomatic samples (sensitivity, 76 percent; specificity, 68 percent). The same study reported that the pooled sensitivity and specificity for ultrasound were 60.8 percent (95% confidence interval, 53 to 68 percent) and 76.3 percent (95% confidence interval, 68 to 83 percent), respectively.

In another meta-analysis⁹, which included 18 studies of MRI for detecting silicone implant ruptures, reported the summary sensitivity to be 78% (95% confidence interval 71 to 83 percent) and specificity 91% (95% confidence interval, 86 to 94 percent). The positive predictive (PPV) value of MRI varies from 50 to 100%, and the negative predictive (NPV) value ranges from 70 to 100%. During high prevalence (50%) of rupture, the PPV of MRI in detecting rupture is more than 80%, whereas during situations of prevalence less than 10%, the PPV never exceeds 80%. At high prevalence conditions, the NPV is more than 80%, and at lower prevalence rates of rupture, the NPV always exceed 80%. This level of accuracy appears to be sufficiently high to warrant use of MRI as a diagnostic aid among women with symptomatic breast implants.

⁵ Everson LI, Parantainen H, Detlie T, Stillman AE, Olson PN, Landis G, Foshager B, Cunningham B, Griffiths HJ. Diagnosis of breast implant rupture: imaging findings and relative efficacies of imaging techniques. *Am J Roentgenology* 1994; 163(1): 57-60.

⁶ Ahn CY, DeBruhl ND, Gorczyca dP, Shaw, W, Bassett LW. Comparative silicone breast implant evaluation using mammography, sonography and magnetic resonance imaging: Experience in 59 implants. *Plast & Reconstr Surg* 1994; 94(5): 620-627.

⁷ Scararanelo AM, Marques AF, Smialowski EB, Lederman HM. Evaluation of the rupture of silicone breast implants by mammography, ultrasonography and magnetic resonance imaging in asymptomatic patients: Correlation with surgical findings. *San Paulo Med J* 2004; 122(2): 41-47.

⁸ Ibid, Song 2011.

⁹ Cher D, Conwell JA, Mandel J. MRI for detecting silicone breast implant rupture: Meta-analysis and implications. *Annals of Plast Surg* 2001 Oct; 47(4): 367-380.1

However, the authors concluded that whether MRI should be used among women who are asymptomatic is less clear.

Sensitivity and specificity of these different imaging modalities depends on different factors such as type of rupture, expertise of the radiologist performing and interpreting the study, type of device.

iii. What we have learned from the Core Studies related to MRI

In Allergan’s and Mentor’s respective *Core Studies*, rupture rates varied by device and indication as presented in Tables 5 and 6.

| Table 5: Cumulative incidence of rupture rates among implants in the MRI group at 10 years post-implantation (95 percent confidence intervals), Allergan Core Study | |
|--|-----------------------------|
| 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) |

| Table 6: The cumulative incidence of rupture rates among Mentor implants at 8 years post-implantation (95 percent confidence intervals), Mentor Core Study | |
|---|----------------------------|
| 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; however, depending on the cohort, up to 35 percent of ruptures may be silent.

The panel will be asked to discuss the how compliance with MRI can be increased, considering the schedule for MRI screening and other factors that may increase noncompliance

d. Findings

i. Core and Large Studies

As noted in the white paper (Appendix F), to date, the only new safety concern that has emerged since approval is a was announced in January of this year, noting that the FDA believes that women with breast implants may have a very low but increased risk of developing anaplastic large cell lymphoma or ALCL which was found through routine medical device reporting and literature review (not the PAS studies) Further details of this finding can be found in “Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses” (Appendix G)

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 showed few occurrences of CTD, reproductive or lactation problems, or breast cancer.

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.

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 an association 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.

ii. Device Failure Studies

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

a. 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.

b. 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.

iii. Focus Group Studies

a. Allergan Findings

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.

b. Mentor Findings

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.

iv. Adjunct Studies

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.

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.

v. Post-Approval Studies Summary

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 suggest an association between silicone gel-filled breast implants and CTD, reproductive problems, or breast cancer. Study limitations 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.

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.

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.

e. Coverage Barriers for Recommended MRI Follow-Up

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 screen for silent ruptures event if a women is having no problems with her implant. The labeling also states the following:

“When MRI signs of rupture are found (such as subcapsular lines, characteristic folded wavy lines, teardrop sign, keyhole sign, noose sign), or if there are signs or symptoms of rupture, you should remove the implant and any gel you determine your patient has, with or without replacement of the implant. It also may be necessary to remove the tissue capsule, as well as the implant, which will involve additional surgery, with associated costs. If your patient has symptoms such as breast hardness, a change in breast shape or size, and/or breast pain, you should recommend that she has an MRI to determine whether rupture is present..”

The Women’s Health and Cancer Rights Act of 1988 WHCRA requires all group health plans and health insurance issuers to provide the following coverage for women who undergo breast reconstruction in connection with a mastectomy:

1. All stages of reconstruction of the breast on which the mastectomy has been performed;
2. Surgery and reconstruction of the other breast to produce a symmetrical appearance; and

3. Prostheses and physical complications of mastectomy, including lymphedemas, in a manner determined in consultation with the attending physician and the patient.

Such coverage may be subject to annual deductibles and coinsurance provisions as may be deemed appropriate and are consistent with those established for other benefits under the plan or coverage. Written notice of the availability of such coverage shall be delivered to the participant upon enrollment and annually thereafter. “ (Source: CMS).

Several barriers result in non compliance with the recommendations for MRI screening for implant rupture, including the following:

1. Women who lack health insurance and are not eligible for Medicaid or Medicare must pay for the MRIs themselves
2. The costs of MRI are prohibitive for some women
3. For those who are insured, some group health plans and health insurance plans specifically exclude coverage for screening MRIs to detect ruptures to women who received breast implants for augmentation because breast implant surgery for augmentation is considered an elective and not medically necessary procedure.
4. Some plastic surgeons question the clinical value of screening for asymptomatic ruptures, especially in light of the risk of false positives results from MRI, and the risk of unnecessary explantation surgeries, and their sequelae.

III. Methodological Issues in Future PAS

a. Endpoints

i. Effectiveness

Measures of effectiveness for breast implant procedures can include patient satisfaction and quality of life outcomes. Patient satisfaction can be assessed by asking the woman if she would have the initial surgery again, in addition to questions to about the satisfaction with the shape, feel, and size of the implants. Quality of life is typically assessed using a questionnaire and comprises of measures of self-esteem, body image, and general health outcomes. There are many quality of life scales that exist and are being used in breast implant studies (Rosenberg Self Esteem Scale, the Body Esteem Scale, the Tennessee Self Concept Scale (TSCS), the SF-36, and the Functional Living Index of Cancer). For augmentation patients, effectiveness measures can also include circumferential chest size change and bra cup size change.

a. Methodological Issues for Effectiveness

Methodological issues regarding effectiveness in future postmarket breast implant studies include the following:

1. What is the optimal method to measure effectiveness of breast implants in the postmarket setting?
2. How will effectiveness be determined? (i.e. what threshold of results shows effectiveness?)
3. For how long and how often should effectiveness be assessed in the postmarket setting?

ii. Safety

Safety endpoints for breast implants can include complication rates, adverse outcomes, and other clinical outcomes.

Local complications and adverse outcomes to be measured can include capsular contracture, reoperation (and reasons for reoperation), implant removal (and reasons for implant removal), implant rupture, wrinkling, asymmetry, scarring, pain, and infection. Potential rare complications for which causality has not been established, such as connective tissue disease, breast cancer, lactation complications, reproduction complications, and suicide, can also be measured. Other safety endpoints which can be measured include MRI compliance and post-implantation mammography experience.

Complication rates and adverse outcomes can be measured at the patient level or implant level, by implant indication cohort or implant type, by participant self-report (questionnaire) or investigator report (office visit), and by periodic incidence or cumulatively.

a. Methodological Issues for Safety

Methodological issues regarding safety endpoints in future postmarket breast implant studies include the following:

1. What are the safety endpoints that should be assessed?
2. For how long and how often should safety be assessed in the postmarket setting? Should this vary for different endpoints?
3. What is the preferred method for collecting safety data: participant self-report (questionnaire) or investigator report (office visit)? Does this vary for different endpoints?
4. How will safety be determined? (i.e. what threshold of results show safety?)

b. Designs

- i. Multi-studies to address specific questions
 - a. New enrollment study—tracking known adverse events
 1. With/without CTD assessment

A new enrollment study of women receiving silicone gel-filled breast implants can be conducted to study common outcomes and local complications, such as capsular contracture, reoperation, implant removal, implant rupture, pain, and infection.

In addition, less common disease outcomes can also be captured, including: connective tissue diseases such as rheumatoid arthritis, rheumatic polymyalgia, chronic fatigue syndrome, and fibromyalgia; rheumatologic and neurologic signs and symptoms; suicide/attempted suicide; breast and lung cancer; and reproductive outcomes. If the new enrollment study is powered on

the less common diseases (for example, rheumatoid arthritis with an estimated incidence of less than 50 cases per 100,000 persons), the required sample size would range from 3,000 to 5,000 participants which includes an adjustment for 35% loss to follow-up over 10 years (assumptions of 80% power to detect a doubling (2x) in the baseline rate derived from national norms, and one-sided significance level of 0.05).

Rare disease outcomes can also be captured including all connective tissues diseases, neurological diseases, and all types of cancer. If the new enrollment study is powered on rare events (for example, scleroderma with an estimated incidence rate of 2.85 per 100,000 person-years) the required sample size would be approximately 40,000 participants which includes an adjustment for 35% loss to follow-up over 10 years (assumptions of 80% power to detect a doubling (2x) in the baseline rate derived from national norms, and one-sided significance level of 0.05).

2. Controls

Control groups to be used for comparisons in new enrollment studies can include saline breast implant patients, women undergoing other aesthetic surgery (such as liposuction, face/neck/brow/forehead/breast lifts, rhinoplasty, breast reduction, calf/buttock/cheek/chin implant, abdominoplasty, or body contouring), national norms and population-based disease rates (such as Surveillance Epidemiology and End Results [SEER] data), disease rate estimates from other registries, reference study populations in the literature, or historical control groups.

In order to detect local complication rates at least twice as high in silicone-filled breast implant subjects than in saline-filled breast implant subjects for events with incidence rates of at least 1.2 per 10,000 person years, with assumptions of 80% power for a one-sided test at the 0.05 significance level, the required sample size would be approximately 15,000 control patients which includes an adjustment for 35% loss to follow-up over 10 years, assuming a sample size of 40,000 silicone gel-filled patients in the treatment arm.

In order to compare a 2% difference in the rate of an outcome (for example, rheumatologic/neurologic signs and symptoms) between silicone-filled breast implant subjects (at a 4% rate) and a control group of women undergoing other aesthetic surgery or control group of saline breast implant subjects (at a 2% rate), the required sample size would be approximately 750 control patients which assumes 80% power, a one-sided test at the 0.05 significance level, and includes an adjustment for 35% loss to follow-up over 10 years, assuming a sample size of 40,000 silicone gel-filled patients in the treatment arm. .

b. Secondary study

1. To track CTD and rare outcomes

A new enrollment study could also be supplemented with a secondary study, where the new enrollment study focuses on capturing less common disease outcomes and local complications while the secondary study would be designed to capture rare disease outcomes.

A case-control study could be conducted to include a patient population with the rare outcomes of interest (for example, rare CTDs like scleroderma or systemic lupus erythematosus). Cases would include those patients with the rare outcome or outcomes of interest. Controls would include patients who do not have any of the rare diseases under study. The research hypothesis would be that there is no association between the rare outcome(s) and the presence of the breast implant. Based on a 1% prevalence of the breast implant in the patient population, with 80% power to detect a relative risk of 2.0 and a significance level of 0.05, the case-control study would need to enroll approximately 1,500 cases and 4,000 controls.

ii. Methodological issues in New Study Designs

Methodological issues regarding study designs in future postmarket breast implant studies include the following:

- a. What are the important safety outcomes to capture in new enrollment studies?
- b. What is the ideal study duration for new enrollment studies?
- c. Which control groups should be used in new enrollment studies? -Should this vary for different safety outcomes?
- d. What other study designs outside of new enrollment observational studies can be used for postmarket breast implant studies?
- e. How will confounding affect the use of case-control studies, considering that if there may be exposure to breast implants other than the one that is being studied?

c. Data Sources for PAS

i. Primary Data

Currently, PAS studies are designed to collect primary data in large numbers of women.

ii. Other Data Sources

The long-term safety and effectiveness in the postmarket setting can be studied by utilizing other data sources such as registries and administrative health databases.

a. Registries

Registries can be valuable tools for evaluating safety of silicone breast implants in routine practice. The utilization of these registries can allow prospective or retrospective evaluation of the incidence, severity and long-term consequences of complications as well as rare adverse events such as CTDs, cancer, neurological diseases and reproductive and lactation problem. However, patient registries have several limitations such as quality of the data, challenges in the analysis and interpretation of the data, potential sources of bias and lack of control cohort.

Table 7 shows some of the examples of the existing breast implant registries and cohorts worldwide.

| Table 7: Characteristics of U.S. and International Registries and Cohorts for Evaluating Outcomes of Breast Implant Use | | | | | | |
|--|---------------|---|--|--|--|---|
| Registry | Region | Participants | Enrolled population | Data elements (pre-operative) | Data elements (post-operative) | Length of follow-up |
| Breast implant registry.com | Unknown | Unknown | All women with breast implants – voluntary registration | Procedure, implant and surgical information | Unknown | 7 years, ongoing |
| Canadian CBI Cohort | Canada | Women with CBI and women with other cosmetic surgery as controls | 24,558 women with CBI and 15,893 women with other cosmetic surgery between 1974-1989 | Implant and surgical characteristics | Cancer | Linked to Canadian Vital Statistics Death Database |
| Danish Breast Implant Registry | Denmark | All women seeking breast implantation and women who undergo breast reduction or mastopexy | 5,373 women with cosmetic BI between 1999-2007 | Self-administered questionnaire on medical history, demographic and behavior factors | Surgical data, postoperative results and complications | 3 months – 1 year |
| Danish CBI Cohort | Denmark | Women with CBI and women with other cosmetic surgery as controls | 1,135 women with CBI at public hospitals between 1977-1992 and 1,653 at 8 private clinics between 1973-1995; 8,807 control women | Not known | Health outcomes (cancer, CTDs, et al.) | Linked to various registers including hospitalization, cancer and death registers |
| Finnish CBI Cohort | Finland | Women with CBI | 2,171 women with CBI at 11 participating hospitals and clinics between 1970-1999 | Age | Cancer | Linked to Finnish Cancer Registry |

| | | | | | | |
|---|--|--|---|---|-----------------------|---|
| International Breast Implant Registry | Europe – founded in Turkey, Brazil is also included. | International | Augmentation and Reconstruction | Implant and surgical characteristics | Complications | 7 years, ongoing |
| Los Angeles Augmentation Mammoplasty Study | US | Women with CBI | 3,139 Caucasian women with CBI between 1953-1980 | Unknown | Cancer | Linked to LA County Cancer Surveillance Program Database |
| MHRA National Breast Implant Registry | UK | 280 BI surgical centers in UK | Women with BI in UK | Procedure, implant and surgical information | Complications | Unknown |
| North American Breast Implant Registry (NaBIR) | US | Women with BI | >9,900 implants as of September 2003 | Implant, procedure, surgical information | Complications, cancer | 10 years, ongoing |
| Swedish CBI Cohort | Sweden | Women with CBI | 3,486 women with CBI identified through Swedish National Patient Register between 1965-1993 | Unknown | Health outcomes | Linked to various registers including hospitalization, cancer and death registers |
| US Augmentation Mammoplasty Cohort | US | Women with CBI and women with other cosmetic surgery as controls | 13,488 women with CBI and 3,936 women with other cosmetic surgery between 1962-1988 | Unknown | Health outcomes | Average 11-12 yrs. Mailed questionnaire (demographic factors, health outcome, life-style factors) |

b. Administrative health databases

These databases, especially from countries of single-payer government health insurance systems can be used to address some of the postmarket questions regarding silicone breast implants. Some examples of these databases are administrative health data from most of the European countries, Canada and Brazil. Administrative databases may provide an existing source of longitudinal information on women who have silicone breast implants. However, administrative health databases have several limitations such as quality of the data, the breadth of information collected and potential sources of bias. The lack of unique device identification also limits findings as conclusions can only be drawn on the class of devices such as saline or silicone implants. The specific model or brand of device cannot be determined. Additionally, when data from sources outside the United States are used, variations in demographics, care practices and health care sources may also limit generalizability to the United States.

d. *Bayesian Methods*

Bayesian methods are useful to synthesize data from various sources.

- i. Combining Core study, Continued Access studies, New-enrollment post-approval studies
- ii. Synthesizing across breast implant types for endpoints which are not specific to a particular implant.

Bayesian methods may be useful to synthesize data on breast implants from various sources, using methods such as hierarchical models. For example, these methods could be used to combine results from a Core study, Continued Access studies and New-enrollment post-approval studies provided the studies are judged to be exchangeable and are all of sufficient quality. The combined results will then yield statistically more powerful conclusions. In addition, such methods could be used to synthesize data across breast implant manufacturers for endpoints which are not specific to a particular brand of implant. This latter consideration points to a question for the panel.

IV. Draft Questions to the Panel

The Panel will be asked to discuss the following questions:

1. For future PAS, please, please discuss for each of the endpoints discussed what you feel is the optimal methodology to assess the findings.
 - a. Local complications
 - b. Other known common adverse events
 - c. Rare events without causality demonstrated to date
 - d. Effectiveness
2. Please discuss the utility and role of a registry of all women who receive breast implants.
 - a. Would a registry be a potential option for long-term evaluation of safety and effectiveness of future devices?
3. Please discuss strategies that will increase compliance with follow-up schedules and consider the following:
 - a. Inclusion of stakeholders such as professional societies or other health care providers
4. Should future PAS include the informed decision process and the physician survey?
5. What outcomes should be followed related to CTDs?
6. Regarding Imaging/MRI
 - a. What descriptive data is important for suspected and confirmed ruptures to more effectively capture methods of diagnoses
 - b. How can MRI compliance be increased? Please consider:
 - i. MRI schedule (for each scheduled MRI (percentage of subjects who complied by indication cohort)
 - ii. Addressing reasons for noncompliance (e.g., discontinuation because of claustrophobia).
7. What outcomes can be studied across breast implant types, that is, are not specific to a particular brand of implant. For example:
 - a. Quality of Life/Self-Esteem measures
 - b. Interference with mammography
 - c. Surgery-related outcomes
8. In future post approval studies, what are the most appropriate comparators for nth generation silicone gel-filled breast implants?
9. Please discuss what long-term evaluation is needed for new breast implants when they are similar to currently approved ones.
 - a. An adaptation of a current model
 - b. Slight modifications in design
10. Please discuss the following: Based upon the discussion for future PAS, what improvements do you think should be made in the current PAS studies?