General and Plastic Surgery Devices
General Issues Advisory Panel
Discussion of Silicone Gel-Filled Breast Implants (SGBIs) Post-Approval Studies, the Present and the Future

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Branch Chief
Division of Epidemiology
Office of Surveillance and Biometrics, CDRH/FDA
August 30-31, 2011
Purpose

• Update the panel on the status of the ongoing post-approval studies
• Discuss strategies to evaluate the real-world and long term performance of silicone gel-filled breast implants (SGBIs) after market approval
• Provide transparency and a public forum for discussion
Goals

• Seek recommendations from the panel
  – Design and implementation of new silicone gel-filled breast implant submissions post-approval studies
  – Recommendations for surveillance of ongoing silicone gel-filled breast implant post-approval studies

• Goals of this discussion
  – Identify approaches that will maximize the feasibility and successful completion of mandated postmarket studies.
  – Gain input on innovative approaches to new studies
  – Provide opportunity to hear input the public and interested parties
Regulatory History

1991
• Final rule calling for submission of PMAs for SGBI.
• Advisory Panel meeting to discuss several PMAs for SGBI.

1992
• Voluntary moratorium on SGBI breast implants
• FDA held a second Panel meeting
• Adjunct Study protocol for its SGBI for reconstruction and revision patients only

1999 IOM Report—No evident risks of CTDs for SGBI

2002 Allergan submitted a PMA for its SGBI
Regulatory History Cont.

2003

• FDA Advisory Panel meeting to review Allergan’s PMA for its silicone gel-filled implants
• Mentor submitted a PMA for its silicone gel-filled breast implants.

2005

• FDA Advisory Panel meeting to review Allergan’s updated PMA and Mentor’s PMA

2006

• The FDA approved Allergan and Mentor’s PMAs for silicone gel-filled breast implants
• Promised to update Panel in 5 years
FDA Activities 2011

• Issued a Safety Communication on Anaplastic Large Cell Lymphoma (ALCL) in women with breast implants

• Issued an Update on the Safety of Silicone Gel-Filled Breast Implants

• Panel Update and Discussion
We would like again to thank the panel members for taking the time out of their schedules to help FDA with these issues, as well as the members of industry, professional societies, patients and the general public for coming and presenting their views on this issue.
Update on Silicone Gel-Filled Breast Implants (SGBIs)
Post-Approval Studies
August 30, 2011
Overview

• Overview of Post-approval Studies (PAS)
• Conditions of Approval
• Key Findings from SGBI PAS
• Summary of Preliminary Findings
  − Focus Group Studies
  − Device Failure Studies (Annual Update)
  − Informed Decision Studies (Annual Survey)
  − Continued Follow-up of the CORE (Pivotal Study)
  − Large Post-Approval Studies (New Enrollment Study)
  − Continued Follow-up Adjunct Study participants
• Future Considerations for PAS
• Other Surveillance and Literature
SGBI Post-Approval Studies Required as Conditions of Approval

1. Focus Group
2. Device Failure Study
3. Informed Decision Survey
4. Continued Follow-up of the CORE (Pivotal Study)
5. Large Post-Approval Study (New Cohort)
6. Adjunct Study (Enrollment Closed at Approval)
Key Summary Findings from SGBI Post-approval Studies

Silicone gel-filled breast implants:

- Significant risks of local complications and adverse outcomes
- Long-term findings similar to when approved
  - New finding ALCL
- Continue to be safe and effective if used as intended
- Not lifetime devices
- Benefits and risks are sufficiently well understood to allow informed decisions
## Status of Allergan and Mentor Non-clinical Post-Approval Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrollment</strong></td>
<td><strong>Enrollment</strong></td>
<td></td>
</tr>
<tr>
<td>Focus Group</td>
<td>Closed 52 patients included</td>
<td>Closed 35 patients included</td>
</tr>
<tr>
<td>Device Failure Studies</td>
<td>All returned devices</td>
<td>All returned devices</td>
</tr>
<tr>
<td>Informed Decision Survey</td>
<td>Annual Random sample of 50 physicians</td>
<td>Annual Random sample of 50 physicians</td>
</tr>
</tbody>
</table>
CORE Post Approval Studies
## SGBI Core Studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 year Multi-center, prospective clinical trial, no comparison</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women enrolled in the clinical trials to support premarket approval application (PMA)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study size</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>715 subjects</td>
<td>1,008 subjects</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data collection</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Follow-up Clinic visits: Physical exam, adverse events and self-administered patient questionnaire</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>66% at 10 years</td>
<td>58% at 8 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI Cohort</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Pre-Approval, MRI at intervals or MRI based on symptoms -Post-Approval, MRI at intervals, all patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Indication Cohorts for PAS

• **Primary Augmentation** - increase breast size

• **Revision Augmentation** – correct or improve the results of primary breast augmentation surgeries

• **Primary Reconstruction** – replace breast tissue removed due to disease or trauma or that failed to develop properly

• **Revision Reconstruction** correct or improve the results of primary breast reconstruction surgeries
## Patient Follow-up Goals by Years after Implant Received

<table>
<thead>
<tr>
<th>Years</th>
<th>Target Percentage of Participants</th>
<th>Follow-up Percentage range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96.5</td>
<td>93.0-100.0</td>
</tr>
<tr>
<td>2</td>
<td>93.0</td>
<td>89.5-96.5</td>
</tr>
<tr>
<td>3</td>
<td>89.5</td>
<td>86.0-93.0</td>
</tr>
<tr>
<td>4</td>
<td>86.0</td>
<td>82.5-89.5</td>
</tr>
<tr>
<td>5</td>
<td>82.5</td>
<td>79.0-86.0</td>
</tr>
<tr>
<td>6</td>
<td>79.0</td>
<td>75.5-82.5</td>
</tr>
<tr>
<td>7</td>
<td>75.5</td>
<td>72.0-79.0</td>
</tr>
<tr>
<td>8</td>
<td>72.0</td>
<td>68.5-75.5</td>
</tr>
<tr>
<td>9</td>
<td>68.5</td>
<td>65.0-72.0</td>
</tr>
<tr>
<td>10</td>
<td>65.0</td>
<td>65.0</td>
</tr>
</tbody>
</table>
Allergan Silicone Gel-Filled Breast Implants
Preliminary Results of Core PAS
10 years Post-implant
## Allergan SGBI CORE Study Patient Enrollment

<table>
<thead>
<tr>
<th>Study Population</th>
<th>PA</th>
<th>RA</th>
<th>PR</th>
<th>RR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>455</td>
<td>147</td>
<td>98</td>
<td>15</td>
<td>715</td>
</tr>
<tr>
<td>MRI cohort</td>
<td>147</td>
<td>49</td>
<td>50</td>
<td>5</td>
<td>251</td>
</tr>
</tbody>
</table>

PA: Primary Augmentation  
RA: Revision-Augmentation  
PR: Primary Reconstruction  
RR: Revision-Reconstruction
Allergan SGBI Core Study
Effectiveness at 10 Years

• Most women satisfied with their implants
  – Shape size and feel of implants
  – Body image

• Most physicians satisfied with the outcome
Allergan SGBI Core Study
Local Complications at 10 Years

Number of Patients at 10 Years
- Primary Augmentation (n = 269)
- Revision Augmentation (n = 74)
- Primary Reconstruction (n = 44)
- Revision Reconstruction (n = 8)
Mentor Silicone Gel-Filled Breast Implant
Preliminary Results of Core PAS
8 years Post-implant
# Mentor SGBI CORE Study Patient Enrollment

<table>
<thead>
<tr>
<th>Study Population</th>
<th>PA</th>
<th>RA</th>
<th>PR</th>
<th>RR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>552</td>
<td>145</td>
<td>251</td>
<td>60</td>
<td>1,008</td>
</tr>
<tr>
<td>MRI cohort</td>
<td>202</td>
<td>56</td>
<td>134</td>
<td>28</td>
<td>420</td>
</tr>
</tbody>
</table>

PA: Primary Augmentation  
RA: Revision-Augmentation  
PR: Primary Reconstruction  
RR: Revision-Reconstruction
Mentor SGBI Core Study Effectiveness at 8 Years

- Most women satisfied with their implants
  - Increased breast size
- Positive measures
  - Well-being
  - Self-esteem
  - Body esteem
Mentor SGBI Core Study
Local Complications

Number of Patients at 8 Years

- Primary Augmentation (n = 291)
- Revision Augmentation (n = 77)
- Primary Reconstruction (n = 151)
- Revision Reconstruction (n = 36)
Cautions: SGBI Core Studies

Different designs, cannot compare across studies

• Not designed to estimate incidence of rare diseases (e.g., CTDs) or long-term outcomes

• Not designed to compare silicone gel-filled breast implants to other types of breast implants or other alternatives.

• Low follow-up rates
LARGE Post Approval Studies
# Large SGBI Postapproval Studies

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gather long term information and detect rare events including CTDs, Rheumatologic, Neurologic, Cancer, Suicide, Reproduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 year Multi-center, prospective cohort study with saline control group</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study size</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td>58,995 subjects (39,390 Silicone), Enrollment Closed</td>
<td></td>
<td>41,900 subjects (40,900 Silicone), Enrollment Closed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Allergan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women receiving unilateral or bilateral silicone implants or saline breast implants after November 17, 2006</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data collection</th>
<th>Allergan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic visits: self-administered annual patient questionnaires, MRI per labeling recommendations</td>
<td></td>
</tr>
</tbody>
</table>
## Large SGBI PAS Follow-up Rates

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Implant Type</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOAL</td>
<td>All</td>
<td>96.5%</td>
<td>93.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td>Allergan</td>
<td>Silicone</td>
<td>60.2%</td>
<td>60.5%</td>
<td>†</td>
</tr>
<tr>
<td>Mentor</td>
<td>Silicone</td>
<td>21.8%</td>
<td>24.3%</td>
<td>21.1%</td>
</tr>
</tbody>
</table>

* Calculated as percentage of subjects who had passed the time window for completing that year’s follow-up
† Allergan had not reached 3-year of follow-up

The panel will be asked to consider strategies for improving follow-up rates in PAS studies.
Allergan Silicone Gel-Filled Breast Implant
Preliminary Results of Large PAS
2 years Post-implant
Allergan Large Study Patient Enrollment*

<table>
<thead>
<tr>
<th>Study Population</th>
<th>PA</th>
<th>RA</th>
<th>PR</th>
<th>RR</th>
<th>Missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone</td>
<td>29,886 (72.3%)</td>
<td>6,033 (14.6%)</td>
<td>4,714 (11.4%)</td>
<td>709 (1.7%)</td>
<td>0</td>
<td>41,342</td>
</tr>
</tbody>
</table>

* Percentage that each indication cohort contributes to the total number of participants for each implant type

PA: Primary Augmentation
RA: Revision-Augmentation
PR: Primary Reconstruction
RR: Revision-Reconstruction
Allergan SGBI Large PAS
Local Complications
Mentor Silicone Gel-Filled Breast Implant
Preliminary Results of Large PAS
3 years Post-implant
## Mentor SGBI Large Study
### Patient Enrollment

<table>
<thead>
<tr>
<th>Study Population</th>
<th>PA</th>
<th>RA</th>
<th>PR</th>
<th>RR</th>
<th>Missing</th>
<th>PA &lt; 22 yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone</td>
<td>26,118 (62.2%)</td>
<td>8,365 (19.9%)</td>
<td>5,031 (12.0%)</td>
<td>1,757 (4.2%)</td>
<td>148 (0.4%)</td>
<td>556 (1.3%)</td>
<td>41,975</td>
</tr>
</tbody>
</table>

* Percentage that each indication cohort contributes to the total number of participants for each implant type

PA: Primary Augmentation
RA: Revision-Augmentation
PR: Primary Reconstruction
RR: Revision-Reconstruction
Rates seem higher in the 2 reconstruction cohorts.

Primary reasons at 3 years:
- size change at patient’s request
- infection
- asymmetry

Cumulative incidence highest
- Reconstruction group
- Revision reconstruction group
Adjunct SGBI
Post-Approval Studies
# Allergan and Mentor SGBI Adjunct Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Allergan</th>
<th>Mentor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrollment</td>
<td>Follow-up rate</td>
</tr>
<tr>
<td>Adjunct Study</td>
<td>Closed upon device approval</td>
<td>54% at 1-year, 30% at 3-year, 23% at 5-year</td>
</tr>
</tbody>
</table>
Key Points from SGBI Post-Approval Studies

- Six post-approval studies as conditions of approval
- Longer-term (8 and 10 year) local complications are similar to those observed at the time of approval. Most frequent are:
  - Capsular contracture
  - Reoperation
  - Implant Rupture
  - Implant Removal
Key Points from SGBI Post-Approval Studies (Cont)

- Breast implants are not lifetime devices
- Routine replacements not necessary, however:
  - The longer a woman has SGBI, the more likely she is to experience complications
  - At 8 or 10 years:
    - For primary augmentation patients 1 in 5 require implant removal
    - For primary reconstruction patients 1 in 2 require implant removal
Key Points from SGBI Post-Approval Studies (Cont)

• No apparent association between SGBI
  – Connective Tissue Diseases
  – Breast cancer
  – Reproductive problems

• Associations with rare or long-term outcomes may not be detected with available data
Key Points from SGBI Post-Approval Studies (Cont)

• Direct comparisons of Allergan and Mentor SBI PAS results not appropriate due to differences:
  – study design
  – clinical endpoints and definitions
  – patient populations

• Low follow-up rates limit ability to draw definitive conclusions and to detect rare complications.

• Findings presented based on interim analysis of currently available data.

• Data collection is on-going.
Postmarket Surveillance of Adverse Events (AE) for SGBI

- Goal to identify unrecognized AE
- Medical Device Reporting System (MDR)
- Mandatory by manufacturers
- Voluntary by patients and health providers
  - MedWatch
    - https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
- Postmarket Spreadsheet Reporting (PSR)
Postmarket Surveillance of Adverse Events (AE) for SGBI

- 133 individual MDRs
  - 24 from Manufacturers
  - 25 from User Facilities
  - 84 Voluntary
- Two reports for same patient
  - ALCL
- Overall consistent with expected ALCL
FDA Preliminary Findings: ALCL and SGBI

- Website and report released Jan, 2011
- Possible association between SGBI and ALCL
- Incidence appears very low
- True cause uncertain
- Collaboration with ASPS and registry development
Review of Literature On SGBI

- Most women satisfied
- Most infections in immediate post-op period
- Literature does not support association between CTD and SGBI
- No evidence of cancer, reproductive or lactation difficulties or suicide risk
Methodological Issues in Future Post-Approval Studies for Silicone Gel-Filled Breast (SGBI) Implants

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Epidemiologist
Division of Epidemiology
Office of Surveillance and Biometrics
August 30, 2011
Outline

• Endpoints
• Designs
• Data Sources
Endpoints

I. Endpoints for Effectiveness

• Circumferential chest size change and bra cup size change

• Patient satisfaction
  ▪ Satisfaction with the shape
  ▪ Satisfaction with the feel and size of the implants
  ▪ Whether the patient would have the initial surgery again
Endpoints (Cont.)

I. Endpoints for Effectiveness

• Quality of life
  ▪ Breast-Q
  ▪ Rosenberg Self Esteem
  ▪ Body Esteem Scale
  ▪ Tennessee Self Concept Scale (TSCS)
  ▪ SF-36
  ▪ Functional Living Index of Cancer
The panel will be asked whether it is necessary to measure long term effectiveness and if so, the optimal methods to measure it.
Endpoints (Cont.)

II. Endpoints for Safety

• Local complications and adverse outcomes
  • Capsular contracture
  • Reoperation
  • Implant removal
  • Implant rupture
  • Wrinkling

• Asymmetry
  • Scarring
  • Pain
  • Infection
Endpoints (Cont.)

II. Endpoints for Safety

- Rare complications
  - Connective tissue diseases (CTDs)
  - Cancer
  - Neurological diseases
  - Reproductive and lactation problems
  - Suicide/attempted suicide
The panel will be asked to discuss the safety endpoints that should be assessed, for how long and how often safety should be assessed and whether this varies by endpoint, the optimal method for collecting safety data.
Methodological Issues for Safety and Effectiveness Endpoints

- The optimal method to measure effectiveness
- Safety endpoints that need to be addressed
- The length and frequency of assessments for endpoints for safety and effectiveness
- Threshold for determining or interpreting safety and effectiveness results
Designs

New Prospective Cohort Studies

• Enrollment of new patients for long-term follow-up

• Conducted to study local complications and adverse outcomes

• Designed to capture less common and rare outcomes
Designs (Cont.)

New Prospective Cohort Studies

• Challenges
  ▪ Sample size
  ▪ Comparison group
Designs (Cont.)

New prospective cohort Studies (Cont.)

• If powered on less common diseases such as rheumatoid arthritis with an estimated incidence of less than 50 cases per 100,000 persons, the required sample size would be 2,800 participants

• Sample size calculation:
  • Includes an adjustment for 35% loss to follow-up over 10 years
  • Assumes 80% power to detect a doubling (2x) in the baseline rate derived from national norms
  • One-sided significance level of 0.05
Designs (Cont.)

New prospective cohort Studies (Cont.)

- If powered on rare disease outcomes such as scleroderma with an estimated incidence rate of 2.85 per 100,000 person-years, the required sample size would be approximately 40,000 participants.

- Sample size calculation:
  - Includes an adjustment for 35% loss to follow-up over 10 years.
  - Assumes 80% power to detect a doubling (2x) in the baseline rate derived from national norms.
  - One-sided significance level of 0.05.
Comparision groups in the new prospective cohort studies

- Saline breast implant patients
- Women undergoing other aesthetic surgeries
- National norms and population-based disease rates
  - Surveillance Epidemiology and End Results (SEER) data
- Disease rate estimates from other registries
- Reference study populations in the literature, or historical control group
Comparison groups in the new prospective cohort studies (Cont.)

- To detect *local complication rates at least twice as high* in silicone-filled breast implant subjects than in saline-filled breast implant subjects, the required sample size would be approximately **15,000 control patients**

- Sample size calculation:
  - Based on the events with incidence rates of at least 1.2 per 10,000 person years
  - Includes an adjustment for 35% loss to follow-up over 10 years
  - 80% power for a one-sided test at the 0.05 significance level
  - Assumes a sample size of 40,000 silicone gel-filled patients in the treatment arm for comparison
Designs (Cont.)

New Prospective Cohort Studies (Cont.)

- If powered on *less common diseases* such as rheumatoid arthritis with an estimated incidence of less than 50 cases per 100,000 persons, the required sample size would be 2,800 participants

- Sample size calculation:
  - Includes an adjustment for 35% loss to follow-up over 10 years
  - Assumes 80% power to detect a doubling (2x) in the baseline rate derived from national norms
  - One-sided significance level of 0.05
Designs (Cont.)

New Prospective Cohort Studies (Cont.)

- If powered on *rare disease outcomes* such as scleroderma with an estimated incidence rate of 2.85 per 100,000 person-years, the required sample size would be approximately *40,000 participants*.

- Sample size calculation:
  - Includes an adjustment for 35% loss to follow-up over 10 years.
  - Assumes 80% power to detect a doubling (2x) in the baseline rate derived from national norms.
  - One-sided significance level of 0.05.
Designs (Cont.)

Comparison groups in the new prospective cohort studies

- Saline breast implant patients
- Women undergoing other aesthetic surgeries
- National norms and population-based disease rates
  - Surveillance Epidemiology and End Results (SEER) data
- Disease rate estimates from other registries
- Reference study populations in the literature, or historical control group
Designs (Cont.)

Comparison groups in the new prospective cohort studies (Cont.)

- To detect *local complication rates at least twice as high* in silicone-filled breast implant subjects than in saline-filled breast implant subjects, the required sample size would be approximately *15,000 control patients*

- Sample size calculation:
  - Based on the events with incidence rates of at least 1.2 per 10,000 person years
  - Includes an adjustment for 35% loss to follow-up over 10 years
  - 80% power for a one-sided test at the 0.05 significance level
  - Assumes a sample size of 40,000 silicone gel-filled patients in the treatment arm for comparison
Designs (Cont.)

Alternative Studies

• Can supplement new prospective cohort studies that can be designed to capture rare disease outcomes

• A case-control study that includes a rare disease outcome of interest such as rare CTDs like scleroderma or systematic lupus erythematosus
Designs (Cont.)

Alternative Studies

• To address that there is no association between the rare outcome(s) and the presence of breast implant, **1,500 cases and 4,000 controls** would be required

• Sample size calculation:
  • Based on a 1% prevalence of the breast implant in the afflicted population
  • With 80% power to detect a relative risk of 2.0
  • A significance level of 0.05
Methodological Issues for Study Design

- Study questions that need to be addressed
- Study design
- Safety and effectiveness endpoints that need to be assessed
- Comparison group (if any)
- Inclusion of specific patient population
- Duration of the follow-up period
The panel will be asked to discuss study designs for future PAS for long-term postmarket safety and effectiveness
Data Sources

I. Primary Data
II. Registries
III. Administrative Health Databases
IV. Medical Records
Data Sources (Cont.)

I. Primary Data

Studies that collect data from women with silicone breast implant on long-term safety and effectiveness
II. Registries

- Valuable tools for evaluating safety of silicone breast implants in routine practice
- Possible long-term data available for
  - Local complications
  - Rare adverse events
Data Sources (Cont.)

II. Registries-examples:

- Canadian CBI Cohort
- Danish Breast Implant Registry
- International Breast Implant Registry
- North American Breast Implant Registry
- Swedish Breast Implant Registry
- US Augmentation Mammoplasty Cohort
II. Registries—Limitations

- Quality of data
- Lack of control cohort
- Potential sources of bias
- Voluntary nature of most registries
- Challenges in the analysis and interpretation of the data
Data Sources (Cont.)

III. Administrative Health Databases

• Address some of the post-market questions regarding silicone breast implants

• Existing source of longitudinal information on women who have silicone breast implants

• Administrative Health Databases from most European countries, Canada and Brazil
Data Sources (Cont.)

III. Administrative Health Databases-Limitations

• Quality of data
• Breadth of information collected
• Potential sources of bias
• Generalizability to the US population
• Limitations due to lack of unique device identifications
Data Sources (Cont.)

IV. Medical Records

• To assess the outcome of interest
  • Less common disease
  • Rare diseases
Data Sources (Cont.)

IV. Medical Records-Limitations

• Not designed to study the outcome of interest

• Data collection is not systematic
Bayesian Methods

• Synthesis of data from various sources using methods such as hierarchical models
  • Combining Core study, Continued Access studies and New prospective cohort studies
  • Synthesizing data across breast implants manufacturers for endpoints that are not specific to a particular brand
The panel will be asked to discuss the other data sources outside of primary data that could be used, and the use of Bayesian Methods to synthesize data from various sources.
FDA Presentation Summary and Questions
Summary of FDA Presentations

• Update on PAS
  – Similar patterns as findings at time of approval
  – No new safety concerns except rare ALCL
  – Low Follow-up
  – Variation in reporting and designs
    • Comparisons across findings limited
**Enrollment Challenges**

**SGBI Large PAS**

**Problem**: Low physician & patient enrollment rates

**Actions Taken**:

- Mentor changed study participation from mandatory to voluntary
- Allergan consolidated 4 study protocols and forms into 1 study protocol and related forms
- FDA supported these changes

**Impact**: Improved and completed enrollment
FDA Actions to Increase Follow-up in Allergan and Mentor Large PAS

• Allergan
  – More frequent contact with study participants
  – Increased incentive to study participants
  – Conducted focus groups of study participants

• Mentor
  – 40,000 Mentor study participants received FDA letter encouraging participation in PAS
    • FDA Received 400+ communications
    • Identified reasons for loss to follow-up
    • Mentor modified webpage
FDA Actions to Increase Follow-up in Allergan and Mentor Large PAS: Impact

**Impact:**

- Improved understanding of factors affecting follow-up rates
- However, little impact on follow-up rates
- Challenges remain
Considerations for Current and Future PAS

- Explore additional retention strategies
  - Contact other physicians (primary, ObGyn)
  - Develop novel patient reporting mechanisms (e.g. social networks)

- Leverage data from existing registries outside the US

- Statistical simulation models

- Power study for more common endpoints

- Use other methodology to detect rare events e.g., ALCL
FDA Questions
1. Given the status of the current clinical post-approval studies (Core and Large) and the challenges that have been encountered in both enrollment and long-term follow-up, please discuss:

   a. Do you agree with FDA’s future considerations regarding the current studies?

   b. What changes, if any, do you think should be made in the current PAS studies?

   c. Is it appropriate to assume a loss to follow-up rate of 35% over 10 years?
2. In future Post-Approval Studies for silicone gel-filled breast implants, please discuss:
   a. Is it necessary to assess long-term effectiveness?
   b. If so, how should it be measured (e.g. device survival, patient satisfaction, etc)?
3. In future Post-Approval Studies to evaluate the long-term safety of silicone gel-filled breast implants, please discuss which long-term safety endpoints that should be assessed.
4. When considering the design of future Post-Approval Studies to evaluate the long-term postmarket safety and effectiveness of silicone gel-filled breast implants, please discuss:

   a. The strengths and weaknesses of different study designs (e.g., new prospective cohorts, registry, use of administrative databases, case-control designs (prospective or retrospective), Bayesian methods) considering:
1) Safety endpoints to be evaluated and whether the design should vary by endpoint;
2) The optimal data sources for collecting safety data;
3) Duration of follow-up necessary;
4) Control/comparison groups;
5) Inclusion of specific patient populations;
6) Outcomes that can be assessed by aggregating data across manufacturers and across breast implant types (not specific to a particular brand or implant);
7) Outcomes that can be assessed for a given manufacturer by aggregating data across breast implant styles.
4. b. When considering both current and future Post approval study designs for silicone gel filled breast implants, please discuss methodologies And strategies that will increase compliance with:

1) Enrollment
2) Follow-up clinic visits
3) Annual questionnaires
4) MRI Screening
5. Please comment on the current scientific data available regarding recommendations about MRI screening for silent rupture in the approved product labeling.
6. Please discuss whether the following conditions of approval, in addition to clinical studies, are recommended to evaluate the postmarket safety and effectiveness of new devices in future post-approval studies:

a. Informed Decision Process studies
b. Device Failure studies
c. Focus Group
7. In future Post-Approval Studies of other breast implants that utilize the same technology as implants already approved, please discuss:

   a. What postmarket evaluation is needed for newly approved breast implants that are similar to currently approved implants?

   b. How should new styles/procedural techniques of the same technology be incorporated into an ongoing, mandated post-approval studies?

   c. What are the most appropriate comparators, if any, for nth generation breast implants of the same technology?
8. Please discuss the unique contributions that groups other than FDA can make to implement and maintain improvement strategies for current and future post approval studies of silicone gel-filled breast implants